

ACTIV, Therapeutics-Clinical Master Protocol Subgroup, Meeting Minutes

Friday, May 22nd, 2020

- (b) (4), (b) (6): *The next version of the protocol we get we will review and send you comments where you centralize all the comments? Will we be able to see all comments to resolve via conversations?*
 - Stacey Adam: I will compile the comments and the commented protocol will be what we work off of. We will be discussing conflicting comments during the writing.
- (b) (4), (b) (6): *Any public announcement planned? Yes. An announcement will be made, but I haven't heard anything yet on the timing. We want to get the site on board before making any announcement. We also may need to have a contract underway.*
 - (b) (4), (b) (6): *Contract would depend on the network selection? Yes.*
 - (b) (4), (b) (6): *The need for support with regulatory agencies, with other countries, would depend on the network? Hoping to stay with an NIH network and have the sponsor hold the IND and companies sign cross-referencing letters to the IND for the master protocol. Outside of US would depend on the sites we decide to open up to.*

Chatbox

From (b) (6) to Everyone: 02:19 PM

TIN uses the CTSA hubs, which is US only. There are 60 hubs. - all of which have a TIN liaison. The hubs all have affiliates, so the TIN represents hundreds of potential sites.

From (b) (4), (b) (6) s iPad to Everyone: 02:19 PM

hi peter, how are you?

High-Level Meeting Summary

The Agent Prioritization Committee (APC) of the Therapeutics-Clinical Working Group (TX-Clinical WG) reviewed progress toward clinical trials of previously selected agents and discussed plans for its second wave of agent prioritization.

A summary of key discussion points follows.

Progress toward Clinical Trials

Participants reviewed progress toward clinical trials for agents prioritized during Wave 1 and for mAbs. For both sets of trials, ACTIV must determine what entity will formally hold Investigational New Drug (IND) applications. To preserve neutrality and support financial logistics, ACTIV prefers that INDs be held by an entity *other than* a pharmaceutical company (e.g., an NIH Institute or Center). Drs. Carl Garner and Peter Stein suggested that a lead academic trial site, academic research organization (ARO), or contract research organization (CRO) could hold an IND, provided that it had experience with safety reporting requirements.

ACTIV-1 Immunomodulator Trials

Trial Network

The TX-Clinical and Clinical Trial Capacity WGs are exploring the possibility of conducting immunomodulator trials using the Trial Innovation Network (TIN), an initiative within the Clinical Translational Science program (CTSA) at the National Center for Advancing Translational Sciences (NCATS). Because some regulations governing the NCATS TIN prevent it from holding INDs, its selection would require a CRO to fill that role.

Participants debated whether research institutes that participate in a CTSA program are qualified to conduct ACTIV trials. Drs. David Goff and John Mellors suggested that these institutes tend to work as individual units on investigator-initiated clinical and translational research, rather than on large multi-center trials. Dr. Elizabeth Higgs recommended that NHLBI networks be considered for ACTIV-1 and suggested that asking networks to simulate enrollment could provide information useful to the selection process.

Company Negotiations

All three companies that own agents selected during Wave 1 have committed to enroll them in ACTIV-1 trials. Those firms are drafting their components of the master protocol, which will be synthesized with previously-drafted statistical components during the week of May 25.

Inpatient mAb Trial Networks

Members of ACTIV met this week with leaders of INSIGHT and PETAL to assess them as potential networks for inpatient mAb trials. Deliberations are closely assessing each network's actual site capacity and approach to holding INDs. The two networks could also theoretically partner, which would allow PETAL's broad reach within the U.S. to complement INSIGHT's global network.

Landscape Tracker

The Hever Group is orchestrating efforts to develop a landscape tracker of anti-COVID-19 efforts. Dr. Sarah Read suggested that the APC develop a contingency plan in case that effort does not align with the timing of Wave 2 Agent Prioritization. Members agreed to complete agent scoring without a landscape analysis and then to ask the (b) (4) (b) (4)) to act as a third-party broker soliciting information related to prioritized agents.

Request for Information for Wave 2

ACTIV is nearing the launch of the REDCap-based Request for Information (RFI) about agents under consideration for ACTIV trials. Designers are adjusting the survey's branching tree structure, which will route respondents to the correct questions.

Agent Prioritization Wave 2

The APC has finalized the sequence and weighting of scoring criteria for Agent Prioritization Wave 2, and Dr. Adam is finalizing an initial list of agents for consideration based on public databases, the NIH public solicitation, and an ongoing review to avoid duplication of external efforts. Participants briefly reviewed the list of agents submitted through the NIH website and did not find any that warrant greater proactive effort to secure RFI responses.

The APC also reviewed their approach to the first round of agent prioritization, in which sub-teams of expert reviewers will assess candidate agents.

mAb Sub-Team

MABs will be reviewed by a team of volunteer experts from (b) (4) , the National Institute of Allergy and Infectious Diseases (NIAID), (b) (4) , and academia (the Executive Committee may recommend other members). The team is establishing *minimal master protocol entry* rather than *prioritization* criteria: it will recommend to the APC minimum thresholds for mAbs to enter a master protocol, and any that do meet the threshold will move to trials. Dr. (b) (6) noted that the (b) (4) is developing standardized monoclonal antibody assays and reference labs that may assist the mAb sub-team. He will send further information to Dr. Adam.

Antiviral, Immunomodulator, and Supportive Therapy Sub-Teams

The APC will collectively adjudicate assignment of specific agents to the three major agent classes under consideration (i.e., antivirals, immunomodulators, and supportive therapies). Each class will then be circulated to distinct expert sub-teams, who will report to the full APC their recommendations of agents for further scoring.

Next Steps

Dr. Adam will circulate tentative sub-team assignments for confirmation by members. The mAb sub-team will meet next Tuesday and the full APC will meet later in the week to discuss an mAb master protocol and potentially adjudicate assignment of agents to class-based sub-teams.

Appendix A: Participants List

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, VP, *Global Regulatory Affairs, Eli Lilly*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Diseases and Stroke (NINDS)*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS)*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical mAb Outpatient Writing Team Meeting-3, Key Takeaways

Wednesday, May 20th, 2020

Action Items

Action Items		
	Information	POC
1	Follow up guidance on adequate safety parameters to ensure site capacity is adequate from FDA perspective	(b) (6)
2	Follow up feedback, re: full resuscitation capacity vs. ability to transport to emergency room with basic life support	(b) (6)
3	Feedback on endpoints and timing (for virology endpoint in Phase II, if there's real-time data, need to decide whether to use one central lab for all studies)	mAbs Steering Committee
4	Share data regarding cutoffs	Ajay Nirula
5	Share document from (b) (6) (which discusses (b) (5))	Stacey Adam

Notes

- From FDA (b) (6):
 - Safety data will be very important in this trial, particularly in Phase II for this protocol.
 - FDA is (b) (5)
 - (b) (5)
 - (b) (5)
 - For most sponsors that FDA has talked to so far, (b) (5).
 - (b) (5)
 - (b) (5)
 - (b) (5)
- Group discussion
 - Question regarding having to look at the quantitative viral data during the course of the Phase II component, which would require someone seeing unblinded information. If the quantitative viral assay turns out to be reproducible and valid, there may be a signal of

Wednesday, May 20th, 2020

activity that merits Phase III before we get to 110 per arm. In Phase II, does FDA ever do futility look or early look for success?

- Depends in part on the phase of the study and the regulatory intent
- If a company has done a 30-patient study, we could still enroll them in our Phase II, and they just might be able to graduate faster. Needs further discussion. Also, need to think about whether someone can skip our Phase II and come into Phase III?
 - This could be doable, but company would need to discuss this with the Steering Committee.
- Can we get a company who's coming right out of animal study and hasn't been in human yet, if they're doing other PK things on the side, can they come into our study?
 - Usually, they would've done a single ascending dose study, and that would be easier to do in the hospital setting.
 - Depends on whether you will do dose finding. They'll usually move right into a placebo-controlled dose finding study. Usually there's more than 2 doses at play. That's a design issue for ACTIV to decide.
- Suggestion to look at what we are proposing in terms of safety monitoring is adequate. Do we have consensus?
 - This is a topic that FDA will talk to companies about in the coming weeks.
 - One of the resolutions could be that it's really SAEs and adverse events of special interest that we're interested in in Phase II. FDA is more interested in infusion reactions and big toxicities that would be fairly obvious, and then the question is how many patients to see before moving into a prevention trial? It'll be tough to decide.
 - It may be simply addressed by expedited reporting.
 - Some of the IL-6 protocols have built in an interim DSMB look at a certain point.
- With a formal DSMB look, let's say with 50 participants with some degree of follow up, does that go hand in hand with the idea that you'd pause enrollment at some point? Wonder whether the pace of enrollment would be sufficiently fast.
 - Pausing enrollment was not in FDA's discussion
 - Think that these types of adverse events will be more similar to severe neutropenia; make that adverse events, and we get reports weekly from sponsor, and that may be adequate.
 - That would be easier.
- We don't get blood until 6 days into the infusion – adequate for monoclonal? Too long? We're looking at types of reactions that are more clinically related. We're talking to the person on day 2 and day 4.
 - That's what the FDA thinks – that it's more observed than laboratory based.

Wednesday, May 20th, 2020

- The other thing with company input – what are the clinical settings where these infusions need to be done? What are the adequate safety parameters... need guidance on that to make sure site capacity is adequate for doing this work
 - (b) (6) to follow up
 - (b) (5)
 - (b) (4), (b) (6) from (b) (4) can provide feedback
- For the virology endpoint in Phase II, getting really good consensus on what should be included would be helpful. If there's a need to have real-time data, we need to determine if it'll be done centrally through one lab for all the studies, or if each company will do on their own. **It's a Steering Committee decision. Need their feedback on endpoints and timing.**
 - Right now, we will leave what we have in unless people think we should change.
 - (b) (6) did run it by agency, and people were fairly comfortable
 - Assume when protocol is drafted, will seek pre-IND advice from FDA?
 - Yes, that's what we would do.
- With the futility analysis in terms of safety and getting some initially pharmacodynamic information for monoclonal studies, does that end up with some kind of alpha spending penalty? How does that get written into the analysis plan?
 - We're not using alpha spending given Bayesian design
 - We'd control the error and check the simulation
 - In general, safety and futility don't spend alpha especially if they're not binding
- Does enrollment pause waiting for Phase II analysis?
 - Working group member not a fan of pausing
 - From pharma perspective, if don't need to stop, that'd be great.
 - If an agent comes in and have 3 doses and still have 3 doses at end of Phase II, need to make a decision of at risk with which dose for Phase III? We don't have to wait but need to understand and decide if we do anything with the randomization during that at-risk time.
- Do we have to specify that in the master protocol? Should we say it won't pause and then think about it?
 - Routinely in ACTG studies, have ongoing blinded review
 - If we start earlier than FDA would normally want us to while concurrently other data are occurring in animal/another Phase I study, we may need to pause, hopefully not. But agreement about ongoing safety monitoring
- It's very important to have the right assay, hopefully it's a validated assay, and that the cutoff is validated as well. It'd be nice to have another look with the precision medicine

Wednesday, May 20th, 2020

- experts. **Sandeep Menon can bring in experts from (b) (4)** We need to be careful on how much to make decisions out of the viral load early. We need to discuss this.
- We don't know whether clinical symptoms or virology will predict if people are going to hospital or dying.
 - About the cutoff – colleagues in (b) (4) have looked into it. **Sandeep Menon to follow up with Ajay Nirula offline to make sure on the same page (b) (4) can share the data.**
 - We will do a central lab assay, and if we need to get a group together to do viral quality assurance, it may be useful.
 - Virologic endpoint:
 - Primary: time to resolution; negative PCR
 - Secondary: change in viral load log reduction
 - Area under the curve of all of those values across 28 days
 - All of these are eligible for graduation of the agent
 - Changed criteria to get everyone less than 7 days from symptom onset
 - We have 20% power
 - In the Bayesian setting, need to construct this to be in some sort of probabilistic statement. 20% is the proportion.
 - Other issue – we want 50% in Phase III to be at high risk for progression. We aren't going to be as strict about it in Phase II. Issue – will that affect our safety assessment if we don't include the same high-risk people in Phase II that we plan to bring in in Phase III?
 - May depend on safety criteria special interest
 - The data is going from Phase II to Phase III, we hope, but not the patient
 - The question is about whether older higher risk people will have different safety signal than younger
 - Safety relative to intervention
 - We wouldn't exclude those people, so they'd probably be included, but we won't have a quota to ensure we have enough of them in Phase II
 - We also don't know about who's at risk for progressing to hospitalization – these are best guesses
 - We have interim safety looks for both phases. So we'd have continuous monitoring, DSMB, and if we see something for high risk in Phase III, we can back pedal away from that.
 - FDA perspective – related to this is enrichment based on the different endpoints for Phase II and Phase III. Helpful to have more symptomatic patients for Phase II and more patients at risk for hospitalization in Phase III. Something that FDA has discussed

Wednesday, May 20th, 2020

- We're trying to enrich Phase I for virologic outcomes. Don't think that we know that symptoms are any worse/different by age. We're trying to enrich Phase III for the risk of hospitalization.
- Pause enrollment at the end of Phase II or continue enrollment?
 - Based on what's been discussed on the call, question as to whether the rate of enrollment will be particularly fast. Worried about how easy it is to pull off Phase III.
 - Suggestion to decide how fast we want study to enroll, what's the pace that we want this to get done at, and what that means in terms of pause.
 - **Everyone is in agreement to keep enrolling.**
- Dropping a less effective regimen in Phase III and how to approach that? If accrual is not fast in Phase III, and we have ~5 agents, we have a large study that will take a long time to complete. Do we drop regimens that are performing less well vs. other regimens?
 - Suggestion to drop based on comparison with placebo
 - Worth looking at really aggressive futility stops
- (b) (6) document discussing (b) (5)
: – Stacey to share
 - With epidemics, it's really hard to share over time
 - It's a real issue in the hospital setting.
 - In the outpatient setting, maybe less of an issue
 - Enrollment will move around different hotspots over time. Possible that virus evolves differently in different locations. For symptom outcomes, different populations, even sex distribution, will affect symptom duration assessment (as in international HIV symptom evaluations).
 - **With companies interested in international sites, we can come back to; this is a big issue**
- (b) (6) (b) (5)
 - We're being fairly simple with our randomization
 - We don't have persistent health biomarkers to know which drugs work with whom
 - We're going with straight up randomization

Chatbox

From Sandeep Menon to Everyone: 06:27 PM

do we know how much is the viral load is correlated to the clinical endpoint ?

ACTIV, Therapeutics-Clinical mAb Outpatient Writing Team Meeting-3, Key Takeaways

Wednesday, May 20th, 2020

It will drive the go/no-go criteria

We should not pause for safety as well

Perhaps have a real time safety monitoring in a blinded way.... Which is not very uncommon

From Davey Smith to Everyone: 06:28 PM

We do not know how much of a correlation there is with viral loads and symptoms

From Sandeep Menon to Everyone: 06:29 PM

Need to ensure we are all sure about the assay?

And the cut off

we are depending on that...

From Davey Smith to Everyone: 06:38 PM

Sandeep do you have a assay that you think we should use across the whole trial?

From Sandeep Menon to Everyone: 06:39 PM

We have been thinking about a quantitative assay internally, but need to check with our PM lab colleagues. Happy to check and get back to you Davey.

From Davey Smith to Everyone: 06:40 PM

Excellent. We would be VERY interested in help with that.

From Sandeep Menon to Everyone: 06:40 PM

Ok, let me get back on that one by tomorrow.

From Sandeep Menon to Everyone: 06:48 PM

If we have agents coming in at different times, very tricky to pause between phase 2 and 3.

thanks Lisa. You articulate my comments better than me !!

From Imlavange to Everyone: 06:49 PM

Sandeep - your chat comments are extremely helpful!

From Sandeep Menon to Everyone: 07:00 PM

Karen — are the regulators fine with the multiplicity? Assuming that we are using non-informative priors we can also show type I error control, was curious to know if we have some early agreement from FDA on multiplicity.

ACTIV, Therapeutics-Clinical Agent Prioritization Subgroup, Key Takeaways

Thursday, May 21st, 2020

Action Items

Action Items		
	Information	POC
1	Schedule upcoming sub team meetings	Stacey Adam
2	Share information with Stacey Adam on La Jolla COVIC work	Michael Vincent
3	Send list of everyone who is on the different subgroups	Stacey Adam/ Elizabeth Kim

Notes

mAbs master protocols and networks

- Continuing to find lead network for inpatient mAbs protocol
- Outpatient mAbs will be led by ACTG, likely with supplemental support. We are already working closely with them. Target to have ready for Steering Committee review next Wed., 5/27.
- Met with INSIGHT and PETAL. Both networks have advantages/disadvantages. Important questions we are considering are their actual site capacity and strategy for holding IND.
 - PETAL predominantly US-based with broad global reach through other NHLBI networks
 - INSIGHT has much more global reach.
 - We will see if we can partner the two together.

Immune modulators network logistics

- Network logistics for immune modulators – we are speaking with NCATS TIN (Trial Innovation Network). NCATS does not generally hold IND for trials, so we need to find a way to do that. Potential for CRO to manage the trial and hold the IND.

Landscape trackers

- Landscape trackers
 - Sensitivity around the BARDA tracker which potentially has proprietary information
 - Update from Executive Committee that HEVER is proceeding with their tracker, will make available to us when ready
 - Suggestion for different approach – when we have a number of prioritized agents, go through BARDA to ask BCG for specific tracker related to each prioritized agents, and do our due diligence at the end?

Company engagement

- All 3 companies for ACTIV-1 are on board: (b) (4).

ACTIV-1

- We have a new version of ACTIV-1 with stats. Each of the companies is getting their piece of protocol by end of the week. By next week, should have all of the pieces together.

INDs

ACTIV, Therapeutics-Clinical Agent Prioritization Subgroup, Key Takeaways

Thursday, May 21st, 2020

- Companies should not hold the INDs. Would be easier for one of the NIH ICs to hold IND / or a neutral third-party broker. For NHLBI, have one of the lead academic sites hold the IND.
 - NHLBI is contemplating setting up a few different AROs and CROs for any clinical trials related to COVID-19.

NCATS TIN

- Would be helpful to know more about NCATS TIN
 - Run across the CTSAs (clinical translational science awards organizations) that NCATS holds
 - NCATS not allowed to hold the INDs
 - Need to do more learning on how they'd manage something like ACTIV-1
 - Better fit for purpose for earlier phase trials given how CTSA's have evolved?
 - There's flexibility.
 - TINs were set up not to run trials but to facilitate other trials.
 - In last iteration, set up 4 centers around the country to get in the business of running trials. One at Hopkins and three others around the country. They're now working to run trials.
 - CTSAs are 60 academic sites around the country. Highest level clinical trial sites around the US. Train people to run clinical trials. Some have inpatient beds for research. Have statisticians, coordinators, etc. Would be worth talking to them to see if they can have some of their sites run the trials. Wouldn't have to be NCATS running the trials but one of the clinical trial sites in the CTSA and then organizing throughout the other 60 university sites.
 - They haven't done a large multi-centered trial in the past.
 - Univ. Pittsburg CTSA is funding COVID-research but has no capacity to do clinical trial.

Moving Into Wave 2 of Agent Prioritization

- We are refining our initial lists, double-checking public databases, have had outreach from other groups like in the UK.
- We have ideas submitted from companies and investigators to NIH and FNIH for consideration.
 - We will reach out to them with the survey by the end of this week.
- Sub-Teams review
 - Antivirals, immune modulators/host-targeted, symptomatic/supportive, SARS-CoV-2 Neutralizing Monoclonal Antibodies
 - Work offline, individuals meet in sub teams and then report out to Agent Prioritization Subgroup
- Mike Vincent share information with Stacey Adam on La Jolla COVIC work.
- Review Subteams
 - Antivirals:
 - Ruxandra Draghia-Akli
 - Libby Higgs
 - John Mellors

ACTIV, Therapeutics-Clinical Agent Prioritization Subgroup, *Key Takeaways*

Thursday, May 21st, 2020

- Host Targeted/Immune Modulators
 - Eric Hughes
 - Elliott Levy
 - Naimish Patel
 - Keith Gottesdiener
 - Mike Vincent
 - Peter Wung
- Symptomatic/Supportive
 - Sarah Read
 - Tim Buchman
 - Walter Koroshetz
- SARS-CoV-2 Neutralizing Monoclonal Antibodies
 - Amanda Peppercorn
 - John Mellors
 - Sebastian Breuer
 - Andrew Adams
 - Flavius Martin
 - Mary Marovich
- Currently unassigned members
 - Libby Higgs
 - David Goff

ACTIV, Therapeutics-Clinical Master Protocol
mAbs Steering Committee - ACTIV2 Synopsis Review
Key Takeaways

Wednesday, May 20th, 2020

Action Items

Action Items		
	Information	POC
1	Reach out to INSIGHT and NHLBI/PETAL to confirm their interest in collaborative approach	Sarah Read, Eric Hughes, and Stacey Adam

Notes

Synopsis

- Judy Currier provided overview of synopsis
- Peter Stein: Idea is to get 50% of patients or more would have a risk factor age or co-morbidity? For Phase II and Phase III populations?
 - Judy Currier: Yes. Would be nice to have for Phase II but required for Phase III. So, it might be a gated strategy where it's not an absolute requirement for Phase II but required for Phase III
 - Peter Stein: Phase II endpoint may not necessarily differ in those populations whereas in the Phase III endpoint you'd need the enriched populations presumably to get the adequate power to see the benefit in the Phase III endpoint. I don't know in the populations brought into the study, may vary by site, what the distribution of the population would be. Concern around the Phase II would be if the greater than 50% requirement ends up being a hindrance to recruitment. We may have to think about the impact recruitment-wise would be.
 - Judy Currier: Yes, while we'd like to have it, we don't want to require it for Phase II because we don't think it will affect the Phase II endpoint.
 - Joan Butters: Potential impact on safety
 - Peter Stein: We want to have some patients with comorbidities coming into the study. The question is what the actual distribution of patients would be – whether it's stratified and restricted to a certain proportion or whether you just leave it open.
- Lisa LaVange: Are you going to learn anything in Phase II that will inform the adaptive enrichment, or do you know everything you need to know about the enrichment before they enter the trial?
 - Judy Currier: It's the latter.
- Lisa LaVange: That worries me about changing the population. I'm worried about wrong dose, safety and tolerability factoring in if they are at higher risk of hospitalization, a few landmines.
- Karen Price: For a Phase II endpoint in terms of being able to show difference on virology endpoint, the symptom onset is the key differentiator. You want to have patients as early as you can from the time there is symptom onset. Phase II endpoint cares more about symptom onset. Phase III endpoint cares more about risk of hospitalization, which is the enrichment element.

Wednesday, May 20th, 2020

- Once the patients qualify for Phase II, they're done before Phase III starts. Phase III would be totally different patients. In the early Phase II, if you take patients who are less than or equal to five days from symptom onset, some will have co-morbidities, and those events could count in that Phase III part from an inferential perspective. But if we were truly picking dose based on virology, you'll get the best information based on symptom onset.
- Libby Higgs: One approach to consider is including individuals who are at high risk or positive but not yet with symptoms. Right now, we don't have that population. That would be a patient group of interest to us eventually. We would want to treat them as early as well to curtail viral replication.
- Janet Woodcock: That might be something that's a very similar trial carried out – like nursing home in high risk populations where there's a lot of positivity before people "crash" because they're all being screened.
- Judy Currier: We specified that it's onset of symptoms and not test because there may be people tested early and then develop symptoms. We'd hate to exclude them if they're within this onset of symptoms.
- Libby Higgs: Take these high-risk people that have the comorbidities, etc. Once they test positive even before they have symptoms, allow them to enter into the study.
- Judy Currier: This is the other tension – the relationship between the onset of the symptoms and the virology. We have tension between the team and some stakeholders around this point of just how short that window is where you have the chance to really see the virologic effect, and it seems really linked to the onset of symptoms. I think we wouldn't want to start dosing people who don't have symptoms because we may miss that.
- Joan Butters: If your endpoint is improvement of symptoms, you have to have some symptoms to start with.
- Janet Woodcock: That'd be a slightly different trial because you'll be dosing a lot of people who may not get sick. Even among the high risk, a lot of people are positive but never become symptomatic. We ought to consider that it's a slightly different population.
- Peter Stein: Could have that population look at time to transition to viral negative but you'd end up with a heterogeneous study population overall.
- Libby Higgs: Other question is around timing of the detection of viral negativity because we're not doing swabs until 6 days. I think we probably want to see it earlier, want to see an earlier effect. Would imagine we have data from some of the outpatient mild to moderate studies (b) (4) where they were doing more frequent viral testing.
- Judy Currier: We've looked a lot of data available, including from (b) (4). I think we're getting it at the time of enrollment and we're looking for a change. Don't know that we'll completely miss that change. It's all about feasibility and what's practical for the participants that we're struggling with.
- Judy Currier: regarding a question in the chat about the doses. The issue if we have multiple agents - this is not a primary dose finding study in Phase II, so we'd need some information about dose before going into this protocol; but we'd evaluate for its activity. It straddles traditional dose finding in phase II.

Wednesday, May 20th, 2020

- Sam Bozzette: I think we're talking about using this for more than monoclonals. In the main study, if we decide to use this framework to do oral direct antiviral, wouldn't want to have that constraint.
- Judy Currier: It's an option for the companies that want to bring forward more than one dose but not a requirement.
- Sam Bozzette: If we decided to add a direct antiviral and that it will be taken daily for a week – would we be okay?
- Joan Butters: We're mixing up doses and dose levels. Doesn't say anything here about how often you're dosing
- Peter Stein: How many arms are we thinking about at one time being possible in terms of number of doses? You're thinking about limiting to 2 dose levels? How many overall arms/how many monoclonals at the same time can be studied?
- Judy Currier: The number of companies is large, but it sounds like in the timelines from what we've heard, that probably we'd be talking about up to four different agents at any given time. I think we need guidance on what the restrictions should be on the number of doses. I think we need to hear from the companies and understand where the products are in development and to be really clear on what purpose of study is. We need things that are ready to be in a Phase II study with some clinical symptom and virology assessment.
- Peter Stein: Those are the only two endpoints available to the companies as well to determine dose, so if they've done that they've already essentially done the Phase II that we're talking about. We have to align this with what the companies are doing to bring the molecule to this point.
- Lisa LaVange: I think philosophically it's important. The first thing we do is randomize to an agent. We'll never randomize across all the dose arms, so we randomize with equal probability to agent; and maybe have 3-5 of those. Then get randomized to drug or placebo. That drug could be 1-3 doses. That's how it's written now – no more than 3.
 - We need to figure out how to distribute sample size. You won't choose between randomization from low dose on this drug and high dose on that drug. We want the dosing to get done quickly.
 - We could assume 150 people for each agent in Phase II – 100 drug and 50 on placebo. If already know dose, 50 on placebo contributed to the shared pooled placebo group across all agent groups. If you don't know the dose, split the 100 or something, but we need to figure that out and do some simulations. We're hoping to go with Bayesian design to get more flexibility with the success criteria but means sample sizes require simulations.
- Peter Stein: Concern is that if only high dose is effective, you could only end up with 30 patients on the high dose. We can't be underpowered to detect a signal at the effective dose if you don't have that information going into the study.
- Lisa LaVange: You drop the doses early and keep randomizing to the high dose. This isn't a one-time thing.

Wednesday, May 20th, 2020

- Karen Price: We've looked at some simulations, but for the less than or equal to 5 days at symptom onset, at 50 patients per arm, it's well-powered the viral endpoint. So, we could think about what's the block that each agent would get and then initially divide that up. Let's say you have three doses, then have equal allocation across those, within short period of time do an interim, potentially drop an arm, and then reallocate those patients to the middle and high dose. Or it could be set up to go fully to the high dose, depending on what makes sense. We'd be able to play around with it. Since it's randomization to the agent, that company can decide how they want to allocate their patients.
- Peter Stein: That seems complicated. In the context of a master protocol where you're trying to get dynamic dose and efficacy information about the molecule, it's pretty complicated.
- Judy Currier: That's an issue from the ACTIV overall perspective, and we need to decide what's the purpose of protocol, where does it fit in development of agents, and where is it most valuable.
- Libby Higgs: Would there be the possibility of using a virologic endpoint in a run in to determine an optimal dose for a particular agent and then put it into a formal Phase II?
- Sarah Read: Don't think we have time. Need to pick simplest most straight forward route. Favor limiting to 2 or 1 dose as opposed to going through all of these manipulations early on. We need something effective.
- Peter Stein: We have to pick the right dose. It's all about getting the right dose here.
- Judy Currier: Some of the companies that ACTG has been talking to have had different approaches. ACTIV needs to decide on the goal of this study.
- Carl Garner: Biggest mistake we make in drug development is not getting the dose right. We want to make sure that we do get the dose right. We also don't want to overdose too much, or we'll limit the amount of material available. The ability to test two doses to make sure we calibrate against all the other data we have (but not just going with the highest dose) would be helpful.
- Lynn Marks: From the sponsors I've seen in their protocols, they are looking at 2 doses. If they're running their programs in isolations, we should be able to plug them in into this program. If you aren't able to do that, the concern is they'd think that ACTIV protocol would slow them down.
- Carl Garner: If we can get input as soon as possible from other companies that could be involved in early days, it could be really important. We don't want to create something that other companies won't want to join. These patients will be precious.
- Lynn Marks: That's my concern as well from the (b) (4) protocols that I see. The endpoints, decision making, sample size estimates are different. If we don't get their input early and they're heading down those paths, industry might not be receptive to totally adopt someone else's approach.
- Stacey Adam: Requesting feedback from Lynn after (b) (4) is able to speak with CEOs
- Lisa LaVange: We can go from 3 to 2 doses if that would be less complicated but give the option to plan the two doses 50/50/50 placebo low high. If the company is running a more extensive dose finding study, and they settle on a dose, we can drop and keep going assuming we have the two that they wanted.

Wednesday, May 20th, 2020

- Lynn Mark: We'll try to get that as soon as we can.
- Sam Bozzette: Idea of having two levels of evaluation? Having places that do the evaluation we've outlined and places for "evaluation light" where we're looking for endpoints and not as many viral load determinations?
- Libby Higgs: That's really Phase II to Phase III, and we can come back to that.

Selection of the network for inpatient population (PETAL and INSIGHT)

- Stacey Adam: We've talked to INSIGHT and PETAL/broader NHLBI group. Both are very eager. Both willing to lead this. Both have pros/cons:
 - INSIGHT: broader global reach, have a mechanism for NIAID to hold the IND
 - NHLBI: maybe faster in getting up and running in the US; mechanism for international IND through Univ. Minnesota; lets lead academic site for their trials hold the IND
- Sarah Read: We didn't invite the investigators onto the call with NHLBI. Still don't feel like I have a good sense from the investigator perspective for NHLBI. NHLBI relayed that the investigators were very experienced, interested, have the capacity. A little concern about capacity of the sites given the other trials they are doing.
 - Think they both have a lot of positives. Both can likely take this on effectively.
- Carl Garner: One observation from call with NHLBI. NHLBI and Petal are willing to do this, excited, but in complement to everything else they are doing.
 - INSIGHT can make this their number one priority, and we need the network to make this their number one priority.
 - NHLBI – it may not be a top priority.
- Lisa LaVange: INSIGHT may have capacity issue too. They're in high demand. They also have the global reach that PETAL doesn't, but PETAL is leaning on REMAP for some of that global reach.
 - When I talk to the pulmonologists, I get different insights about the disease than when I talk to other specialists. I wonder if that adds anything to have a pulmonary focused trial? Uncertain
- Working Group Member: Could they work together? Who would be the investigators for NHLBI?
- Stacey Adam: Lead network site for PETAL is at Vanderbilt. Vanderbilt would hold the IND.
- Lisa LaVange: They started the hydroxychloroquine trial very quickly. On the PRECISE pulmonary study network, we're using the TIN. It's been fabulous.
- Carl Garner: We have a lot of experience with group at Vanderbilt. They're very good.
- Libby Higgs: With the ORCHID trial, protocol came together quickly but was a long time before they could get sites up. Their site activation may be slow. Other concern – network of networks/coordinating center is all very new and not very tested or operationally working together at this point.

ACTIV, Therapeutics-Clinical Master Protocol
mAbs Steering Committee - ACTIV2 Synopsis Review
Key Takeaways

Wednesday, May 20th, 2020

- Ultimately, they probably have a lot of capacity.
- Sam Bozzette: Both have strengths and weaknesses. Is it possible to somehow use both networks but give one a more significant role? I'm concerned about Jim Neaton's group because they're so overcommitted.
 - I would love if we can get both groups.
- Stacey Adam: We asked both – if your network is not selected as lead, would you still want to work with us? Both seemed amenable.
- Sarah Read: The IND that INSIGHT held for ACTT has to do with issues regarding indemnification and EU laws that prohibit US government from holding IND in the EU. Univ. Minnesota only holds the IND for EU within ACTT, not globally.
- Libby Higgs: Can we check on IND issue? If INSIGHT is lead network, NIAID would have the IND.
- Sarah Read: You'd have to figure that out within NIAID. Outpatient master protocol now within DAIDS is a huge lift.
- Judy Carrier: Having members on protocol writing team in other group will be essential. Point of bringing together pulmonary, cardiology, infectious disease is really helpful.
- Sam Bozzette: Agree. Saying one is US and other is non-US.
- Sarah Read: We need to determine who will be the lead.
- Stacey Adam: Move forward with vote via email.

Chatbox

From (b) (6) to Everyone: 01:06 PM

Why restrict to 1-3 doses of investigational agent? Or am I reading that wrong?

From Stacey Adam to Everyone: 01:08 PM

Sam you are right

it is a bandwidth issue given the number of agents

From (b) (6) to Everyone: 01:16 PM

Reactions:

- strong work!

-why 1-3 doses in the core protocol? what if we want to sue this as the bones for say an oral aNTI-VIRAL?

-evaluation seems very intensive; maybe a "lighter" schedule for some sites

From (b) (6) to Everyone: 01:34 PM

I vote to only enroll symptomatic patients

ACTIV, Therapeutics-Clinical Master Protocol
mAbs Steering Committee - ACTIV2 Synopsis Review
Key Takeaways

Wednesday, May 20th, 2020

sorry to waste time on the dose thing - I totally misinterpreted the language

From (b) (6) to Everyone: 01:41 PM

agree with Sarah

From gilbert.marks to Everyone: 01:56 PM

apologies but I'll need to drop now as I need to join the Industry call with Janet.....wish us luck on protocol sharing!!, Lynn

From Stacey Adam to Everyone: 01:56 PM

thanks, Lynn!

High-Level Meeting Summary

The Agent Prioritization Committee (APC) was briefed on TX-Clinical Working Group (WG) activities following the APC's prioritization of Wave 1 agents. APC members finalized the draft Request for Information (RFI) survey and discussed its implementation. They also discussed the prioritization processes for SARS-CoV-2 neutralizing monoclonal antibodies (mAbs) and Wave 2 agents, including an overarching strategy to undertake both efforts.

A summary of key discussion points follows.

Status Update for ACTIV Wave 1 Post-Prioritization Activities

Dr. (b) (6) provided a brief update of four ongoing efforts: (1) negotiating with pharmaceutical companies; (2) resolving network logistics for immune modulators; (3) identifying lead networks for other Wave 1 agents; and (4) gaining access to landscape trackers.

Negotiations with Pharmaceutical Companies

Dr. (b) (6) reported that ongoing negotiations are progressing smoothly. ACTIV has received confirmation from (b) (4) for the use of (b) (4), respectively, in ACTIV trials. ACTIV will meet with (b) (4) on May 19 to discuss (b) (4) and anticipates no issues with securing its confirmation.

Network Logistics for Immune Modulators (ACTIV-1)

Wave 1 agents were divided into two groups—immune modulators and anticoagulants—with plans to evaluate immune modulators using an expanded ACTT master protocol (MP), ACTT 3. Because ACTT 2 recently launched, the ACTT study team is concerned that the network may not have the capacity to layer an ACTT 3 protocol over the ACTT 2 protocol. The proposed ACTT 3 protocol has been renamed “ACTIV-1,” and the Clinical Trials Capacity (CTC) WG is working to identify another lead network for the ACTIV-1 protocol.

Lead Networks for Other Wave 1 Agents

Anticoagulants, the other priority from Wave 1, will be evaluated under a MP being developed by the National Heart, Lung, and Blood Institute (NHLBI)/National Institute of Neurological Diseases and Stroke (NINDS) team. ACTIV plans to monitor the progress of these agents.

Landscape Trackers

Two COVID-19 landscape trackers are under consideration, one each from the Biomedical Advanced Research and Development Authority (BARDA) and The Hever Group. Dr. Adam reported that ACTIV is working with Dr. Janet Woodcock (FDA) to gain access to the BARDA tracker. In addition, she anticipates an update from the ACTIV Executive Committee following Dr. Francis Collins' meeting with The Hever Group this week.

Request for Information (RFI) Survey for Candidate Therapeutics

Following Wave 1 agent prioritization, the APC emphasized that access to standardized data on candidate compounds would facilitate future prioritization waves. Therefore, the APC

developed an RFI survey to solicit detailed information from manufacturers about candidate compounds. To increase the survey's usability and to maximize consistency of data captured, the RFI survey will be converted into REDCap form that includes dropdown menus, character-limited free text fields, and the ability to upload documents (e.g., COVID-19-relevant publications). Dr. Adam shared the most recent draft of the RFI survey for APC input. Dr. Ruxandra Draghia-Akli recommended addition of a field for epidemiological or observational studies that might be useful in evaluating non-classical compounds (e.g., over the counter medications). Dr. Joseph Menetski suggested an "Additional Observational Data" element with yes/no fields under the "General Information" section. Respondents could then append supporting documentation.

Companies will be encouraged to complete the RFI when they submit a candidate for ACTIV's consideration. For public molecules and those prioritized by the APC prior to the RFI's launch, Dr. Adam asked APC members to identify appropriate contacts to receive the RFI survey. The APC discussed two options for utilizing the RFI: (1) as a selection criterion (e.g., manufacturer interest/commitment) for potential candidates following the initial screening and (2) as a tool to identify additional candidates for screening through a broad announcement (e.g., e-mail, advertisements). Dr. Draghia-Akli recommended a hybrid approach.

Some APC members were concerned that the length and complexity of the RFI survey might lower response rates, particularly if ACTIV (rather than the manufacturer) initiates contact. Dr. Menetski explained that the REDCap RFI survey will be more streamlined than the draft version, which includes all modules necessary to address different treatment modalities (e.g., antivirals, vaccines). Dr. Keith Gottesdiener recommended a two-staged approach to soliciting information, wherein the manufacturer provides a subset of RFI data and then the APC requests additional data if the candidate is selected.

Agent Prioritization—SARS-CoV-2 Monoclonal Antibodies and Wave 2 Agents

In response to ACTIV's letter to the FDA indicating that SARS-CoV-2 neutralizing antibodies (mAbs) were a high priority, Dr. Woodcock requested that MPs for SARS-CoV-2 mAbs be expedited and prioritized. As a result, the APC was asked to assist with prioritization of potential candidate mAbs identified by ACTIV for inclusion in ACTIV-2 and ACTIV-3, which will evaluate mAbs in outpatient and inpatient populations, respectively.

Current Agent Prioritization Landscape

Dr. Adam identified six trials for potential inclusion under the ACTIV umbrella: (1) ACTIV (b) (4) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) using the ACTT-2 MP; (2) ACTIV hiVIG, sponsored by NIAID; (3) ACTIV-1 immune modulators, for which ACTIV is currently negotiating the availability of candidate drugs with pharmaceutical companies and working to identify a new lead network; (4) ACTIV anticoagulants, sponsored by NHLBI/NINDS; (5) ACTIV SARS-CoV-2 neutralizing mAbs; and (6) ACTIV additional agents, which will be studied with the (b) (4). The AIDS Clinical Trial Group (ACTG) has been identified as the lead network for ACTIV-2. For the ACTIV-3 inpatient trial, ACTIV is considering the

INSIGHT Network, sponsored by NIAID, and the PETAL Network, sponsored by NHLBI. The ACTIV-2 and -3 MPs will establish a Bayesian adaptive platform trial with seamless Phase 2/3 design. This approach provides the flexibility to use the same MP for small molecules in the future.

Wave 2 Prioritization Processes

Minimum Standards for SARS-CoV-2 Neutralizing mAbs in ACTIV-2

Because there is currently no limit on the number of agents that can be evaluated in ACTIV-2, the APC agreed to define minimum standards for mAbs (e.g., toxicology data, phase 1 safety data, standardized EC50/IC90 data) rather than create a prioritized list of potential candidates. The APC also agreed it would be more efficient and more informative to convene a small team of experts to consider deep technical issues and to propose minimum standards for mAbs. This 6 to 8 member expert team would include technical experts (from the companies represented on the APC), 1 to 2 individuals from the network that will implement the trials, at least 1 NIH and/or BARDA representative to balance any conflicts of interest, and an individual with bioproduct development expertise to evaluate development characteristics. Dr. Carl Garner suggested the APC consider including a representative from (b) (4). Although it is not an APC member company, (b) (4) is a (b) (4) partner with deep expertise in Ebola and experience working with the Defense Advanced Research Project Agency (DARPA).

The APC identified three areas in which they would like input from the expert team: (1) the attributes of candidate mAbs that must be understood (e.g., development characteristics); (2) the minimum criteria to advance mAbs to clinical trials (e.g., toxicology, safety, EC50 data); and (3) other strategic considerations (e.g., advice on targeting a variety of epitopes on the spike protein versus other targets, on effector functions of mAbs, and on the efficacy of combinations of mAbs compared with single agents). Dr. Peter Stein noted that FDA has provided consistent guidance about the requirements to transition to Phase 2 trials, which could be a good starting point for the expert team's analysis.

The APC will review the team's analysis, taking into account additional non-technical considerations, and will recommend minimum standards, to be relayed to the MP Sub-WG and Dr. Woodcock's team at FDA.

Standardized Information for Deprioritized Wave 1 Agents and Novel Submissions for Wave 2

In addition to publicly available compounds not selected in Wave 1, ACTIV has received approximately 60 to 70 new submissions. Submissions include only basic information, such as the name of the agent, a short description, and the name of the submitting company. New submissions will now receive a response including a link to the REDCap RFI survey. The committee agreed the REDCap survey was the optimal approach to collect critical information to support prioritization of these agents.

Strategic Direction for APC Efforts

The APC discussed two options for its overarching strategy: (1) focus exclusively on mAbs until ACTIV-2 is sufficiently underway, and then revert to other molecules of interest (i.e., Wave 2 agents), or (2) pursue both the mAb and Wave 2 workstreams simultaneously. While the mAb work could occur rapidly, the amount of time needed to develop a comprehensive list of compounds for Wave 2 agent prioritization remains unclear. Further, by leveraging competent trial networks (e.g., ACTG, INSIGHT, and PETAL) and the full resources of the public and private sectors, ACTIV should be equipped to address the full scope of strategic potential for a variety of therapeutics, including potential future studies addressing asymptomatic individuals.

Some members agreed that the APC should tackle both mAb and Wave 2 efforts simultaneously. Dr. Gottesdiener agreed with this concept but expressed concerns about the availability of resources to conduct mAb studies. He stressed that ACTIV's capacity (e.g., the ability to recruit enough patients) is an essential practical consideration and that adequate evaluation of mAbs may require every site available to ACTIV, including remaining ACTT 1 sites. Dr. Higgs suggested that a briefing from the CTC WG about ACTIV's saturation point—including which trial sites are counted in multiple surveyed networks—would aid the APC's decision to prioritize mAbs versus pursuing simultaneous workstreams. APC members also agreed that feedback from the ACTIV Executive Committee was crucial to this decision.

Additional considerations for simultaneous workstreams include how to implement additional agents (e.g., small molecules) in the "ACTIV Neutralizing Monoclonal Antibodies" MP (ACTIV-2 and -3) and whether this MP allows for a multi-domain or multi-factorial approach. In general, participants have viewed a factorial design (similar to REMAP-COVID) as too complicated for ACTIV; however, the agnostic design of the mAb MP should accommodate the inclusion of other agents, as well as the addition of a factorial design if necessary.

Next Steps

Dr. Adam will request that the CTC WG brief the APC on network and site capacity, including overlap of trial sites. Dr. Read will solicit feedback from the ACTIV Executive Committee on whether the APC should focus on prioritization of mAbs or address mAbs and Wave 2 agents simultaneously (i.e., dual workstreams). Regarding the expert team to be convened by the APC, Dr. Adam will request APC members to recommend individuals to serve on the expert team. In addition, Dr. Read will contact NIAID colleagues for recommendations.

Appendix A: Participants List

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Health R&D, Johnson & Johnson*

Carl Garner, PhD, VP, *Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Elliott Levy, MD, *Senior VP, Global Development, Amgen*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Rosa Maria Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Peter Stein to Everyone 00:27:37

I was just going to note that FDA has been giving companies consistent input on requirements for getting into the clinic and transition to Phase 2 (tox, in vitro assays, etc.).

Stacey Adam to Everyone 00:27:57

Great!

Carl Garner to Everyone 00:40:41

Stacey - Did you say you had a list of the SARS-Cov2 antibody programs? If you do not, I can share what I pulled from the public domain. 38 programs.

Peter Wung to Everyone 00:56:13

I apologize if this has been brought up or discussed before, but is there the possibility of using an AI platform in looking at pathways and drug targets to help add a separate "voice" in prioritizing these molecules for the next wave?

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

Action Items

Action Items		
	Information	POC
1	Schedule additional time to cover remaining questions that Michael's team needs on Virologic	Stacey Adam
2	Combine the slides shared today for tomorrow's (5/20) meeting and send to the group to review	Stacey Adam
3	Select a preliminary logical symptom duration to move things forward (e.g., duration presented today)	Michael Hughes
4	Review the comments from (b) (4)	Joseph Eron
5	Ensure there is flexibility in the way the master protocol document is designed	Lisa LaVange and Karen Price

Notes

Stats updates

- Lisa LaVange: Presented synopsis slides – *please refer to slides*
 - I think it's still possible to integrate this with the ACTG protocol. We are thinking about first studying a master protocol. It doesn't have to be limited to mAbs. You build the platform for perpetuity and then let things run. This differs from ACTT-3/ACTIV-1 because it's much earlier stage and may not have been in humans yet – we are much earlier in the pipeline and may not know what doses to use. We can think of seamless phase II phase III trial. If we want to move fast, not stopping in between phases helps you do that. If we can get matching placebo that is great. We need to work that out in the synopsis. We can leave the door open. Then you assign to drug or placebo or you assign multiple doses, we've done this before – sharing across the administration works well for master protocols and even sharing across time. We would like the results to support regulatory submission.
- Karen Price: Presented overarching framework, inferentially seamless phase 2/3 slides - *please refer to slides*
 - We don't assume two start at the same time in this first model, but at some point agent 2 comes in the protocol. We would randomize the patient to the agent and then they are assigned placebo or the drug. Then agent 3 comes in, and the randomization is expanded. If an agent does not graduate, it would end and we would return to the 2 others and then move on.
 - If 2 agents come in at the same time, then you would randomize to the agent in a 2:1 fashion, so we have a 100 in each arm after phase then each drug graduates into the phase 3 portion. If it hits 1 or the other, it goes to phase 3. Sample size is specified through simulations.

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

- Michal Hughes: Agree conceptually with what you described, and it reflects the current protocol. What will be the speeds of enrollment in this trial and what will be the feed to define? If the pace of enrollment is modest this works well, but if it's more, then your ability to feedback into the model and the seamless concept becomes more difficult if you have another 1000 participants enrolled into the trial. What pace of enrollment do we think we can achieve?
- Lisa LaVange: My process would be to set it up so that you do have the adaptations, but it's something we must keep on the design page. We'll have a better feel tomorrow from Janet tomorrow.
- Stacey Adam: Yes, Janet will meet with all the CEOs and will have a summit next week.
- Lisa LaVange: Ambulatory side is not easy to understand. We're looking at each agent with blinders on and not pitting them against each other. The number of agents doesn't make it more complicated, but we must do some fire walling.
- Karen Price: Presented Inferentially Seamless Phase 2/3 slides – *please refer to slides*
 - Sample size per arm and number of arms would be specified in the appendix.
 - The success criteria would look a bit different based on the probability, but that the probability is greater than 90 or 95% then phase 3 is presented.
 - We may want to have some early efficacy or futility. Primary phase 3 endpoint is related to hospitalizations. Final success criteria should be a Bayesian.

Structure of Protocol

- Lisa LaVange: Proposed document structure slides – *please refer to slides*
 - This master protocol is agnostic to agent. Master would include as much detail as possible. An appendix would be added for each agent, so you don't have to revise the protocol for each agent. There will be some basic exclusions we make for safety. If we do a Bayesian approach and have prior information would be agent specific and would go into the agent specific appendix
 - You have more flexibility if you structure your document that way – that would be a strong recommendation for how we structure the master protocol document.
- Joseph Eron: Based on what I know, we aren't going to have safety data for these compounds; so for phase 3 there will be 3 primary endpoint – need to add a "no go" for some level of activity. There will be some threshold for activity.
- Lisa LaVange: Will also have a factor of safety and tolerability
- Lisa LaVange: People are struggling with how to structure these things.
- Judy Currier: The companies with the amount of the drug must consider that the distribution of the study product is dependent on many parts.
- Joseph Eron: I agree, it's challenging, and people don't know how to do these studies. I don't think enrollment will be 50 per week so you have your phase 2 filled in 2-3 weeks. We've heard from our

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

sites if the agent is attractive, it will go through. We have quite a few sites in the middles. In North Carolina, it's a steady flow of outpatients.

- Lisa LaVange: I think of this as 2 arm trials, and then you have blinders on for each agent. I don't know if it's right, but it's different from I-SPY
- Michael Hughes: Arguably the more agents you have, the less you want it to be seamless between 2 and 3. Maybe we can get a sense for the number of agents that will come through.
- Lisa LaVange: The Lilly drug that Karen has been working on has multiple doses. To Mike's point, it's not the same. We are thinking you get randomized within the drug and then within the drug to different doses – it's a nested randomization.
- Joseph Eron: If we have multiple agents – and we might be in a situation where we don't have thousands of patients – is there a hierarchy for a priority graduation? We need your help knowing how much of the design should be included in the master protocol.
- Ajay Nirula: This is an expedited path – we want to show that a lower dose reaches the path to efficacy, so we can provide to more patients.
- Lynn Marks: Where do we go if we have a winner at the end of phase 3? How do we manage companies wanting to come in at the same time? How do we sell the program to companies if this leads to this? If Gilead had not provided remdesivir, it would have been a real problem.
- Karen Price: We can specify the current standard of care in the document instead of placebo as this evolves, and we have a standard of care. The master protocol would set us up in the appendix.
- Lisa LaVange: Even if we can't get a matching placebo, there's no reason to not carry over into phase 3.
- Michael Hughes: In phase 2, the placebo is important.
- Joseph Eron: We don't know if the phase 2 endpoint will predict the phase 3 endpoint, for the first agents that go through this we will have to learn. There's a lot we don't know.

Discussion of Phase 3 Design

- Michael Hughes: Presenting Study Population slides – *please refer to slides*
 - This reflects the practicalities in current COVID screening practices. Having at least one targeting COVID symptom could enroll a patient depending on the severity of the symptoms. Up to 10 days of symptoms
- Lynn Marks: The remdesivir trial would inform that criteria.
- Joseph Eron: The issue there is that there is that the longer you wait on symptoms you don't have a baseline viral load to measure, or there is no difference between placebo and symptom.
- Ajay Nirula: We would like to explore if we could do better. There are logistical things to overcome to accrue that. Bringing rapid testing to bear. 5 days is a good balance in something we could solve logistically.

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

- Davey Smith: I worry about it being too narrow if we don't have it for other agents coming through. You can get stuck in the Tamiflu trap if you can only get someone within 5 days of their onset of symptoms.
- Ajay Nirula: We think the key experiment will be the registrational experiment. Optimizing our ability to see a clinically effect
- Joseph Eron: The biologic thing a signal not a registration
- Judy Carrier: I would like to hear from the experts on these trials.
- Lisa LaVange: You can have a requalification of patients, and it can still be considered seamless.
- Michael Hughes: Presenting Study Population and Efficacy Outcomes slides – *please refer to slides*
 - The variability in the control arm would be 7-14 days. The power would be reduced if the population you enroll is different.
- Karen Price: We've looked at some simulations using Flu-PRO. Could we get a copy of this instrument and work together and think about some of the similar things being looked at for flu while knowing they are different?
- Michael Hughes: That would be helpful. We just don't know how comparable COVID-19 is to an influenza, but I suspect its quite different.
- Joseph Eron: If we get more data from outside sources, one could modify the endpoint.
- Paul K: Do you have the scoring from the ongoing study?
- Michael Hughes: But it has a simpler set of symptoms. It has one simple global question around "do you feel like your health has returned to its pre-COVID level?"
- Davey Smith: Do we need to allow eligibility requirements in a design like this?
- Karen Price: I've typically seen the key entry criteria, but if an asset comes in that shouldn't be tested it might be restricted down. It's possible to say you have less than 7 or less than 10, but you tend to want to restrict down not expand further in an appendix.
- David Wohl: It seems like we're agnostic about which symptom metric to use. Is the current proposal one where we rate the different symptoms?
- Joseph Eron: We need to put something in that makes logical makes sense, and if over time we learn that an AUC is a better metric or learn more about the symptoms, then we modify it. We need to pick and move forward.
- David: Can we pick this symptom duration for now (on the slides)?
- Judy Carrier: We must put something up and keep moving.
- Stacey Adam: We can come back to this topic in the next time, so we have time for (b) (4) to present

Update from (b) (4) and Endpoint Discussion

- (b) (4), (b) (6) Presenting (b) (4) slides – *we will request slides (audio went in an out)*

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

- (b) (4)
- -
 -
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- (b) (4), (b) (6) The viral data (b) (4)
 - (b) (4), (b) (6) : We have more than these 2 views, but I'm still comfortable with a simple (b) (4)
 - (b) (4), (b) (6) : Are these the same people or different people plotted on the graph?
 - (b) (4), (b) (6) : I think few people have (b) (4), and if they do, it's usually 2 time points.
 - (b) (4), (b) (6) We are showing (b) (4).
 - (b) (4), (b) (6) : For your change from (b) (4)

Next Steps and Writing Assignments

- Schedule time to discuss several remaining questions that Michael's team needs on Virologic
- Stacey Adam to schedule next meetings
- Lilly send red lines in the document for ACTG
- DaveySmith: I'm leaning more toward a composite endpoint.
- Judy Carrier: Could we use the synopsis from this current version for tomorrow, or should we make changes before tomorrow?
- Joseph: They will want multiple doses.
- Karen: Come with a combined deck for tomorrow. Stacey will combine and send to the group for review.
- Stacey to make sure Janet has what she needs to go to the companies

ACTIV, Therapeutics-Clinical ACTIV TX-Clinical Neutralizing mAb
Outpatient MP Writing Team Meeting
Key Takeaways

Tuesday, May 19th, 2020

Chatbox

6:28:19 From PRICED : Have the slides been advanced?

16:36:04 From Sandeep Menon : how are we planning to combine the data inferentially? will need to ensure regulatory alignment. have we considered operationally seamless

17:12:52 From Lisa LaVange : I need to leave for another meeting. Thanks to everyone for the excellent discussion!

17:18:04 From Karen : Hi Sandeep — from an inferential perspective we seek to not lose the hospitalization endpoints occurring in phase 2 . operational is also on table but given the lower event rate expected it would be important to utilize that phase 2 hospitalization data if we can

17:27:04 From RUBIND : The seamless inferential design seems more straightforward for an agent with only one dose and would likely gain efficiency. If selecting the best of several doses from Phase 2 and then using hospitalization and death data from Phases 2 and 3 in the final analysis, would there be any kind of shrinkage for account for possible random highs?

17:28:09 From Sandeep Menon : Yes, important to understand exposure overlap between doses before adding several doses of the same drug.

17:29:38 From eron : We overcome the power issue by having a higher sample size 100 per arm

17:31:49 From Michael Hughes : There is an inferential issue but it likely will be a modest issue if $n=100$ for Phase II for a given agent (or the selected dose of the agent), and $n=900$ additional in Phase III (so only 10% information coming from Phase II. Also the impact on inference will be affected (reduced) by the imperfect linkage between the virology/symptoms and hospitalization/death

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group Working Group Meeting, Key Takeaways

Tuesday, May 19th, 2020

Action Items

Action Items		
	Information	POC
1	Send emails to Agent Prioritization Working Group members soliciting representatives for small expert group for mAbs “minimum bar” determination	Sarah Read, Eric Hughes, and Stacey Adam
2	Send ideas submitted by investigators and other external stakeholders link to submit information on agents suggested for evaluation	Stacey Adam
3	Bring Clinical Trial Capacity Working Group to present to the Agent Prioritization Subgroup	Stacey Adam
4	Work with Elliott to get information on Real World Evidence (RWE) sources of data to share with the committee	Elliott Levy and Stacey Adam

Key Takeaways

Updates from Stacey Adam:

- Negotiations with companies
 - Confirmation from (b) (4)
 - Conversation with (b) (4) this afternoon, 5/19 [Post meeting note: (b) (4) has confirmed.]
- Network logistics for immune modulators
 - ACTT-3 now known as “ACTIV-1”
 - ACTT network has capacity concerns given they just launched ACTT-2 last week. They may participate but not sure if they have bandwidth to lead.
 - We’re working with Clinical Trial Capacity Working Group this morning to work through network logistics together.
 - Anticoagulants were handed off to NHLBI/NINDS, though ACTIV will keep track of and keep in touch with them regarding their activities.
- Lead networks for mAbs
 - As of last Friday, we’ve been asked by Janet Woodcock at the FDA to bring forward for a higher priority and faster turnaround master protocols for SARS-COV-2 neutralizing monoclonal antibodies.
 - Master protocol group is now designing ACTIV 2 (outpatient) and ACTIV 3 (inpatient) protocols for the SARS-COV-2 neutralizing monoclonal antibodies.
 - There are 21 companies. Some of the prioritization will happen organically.
 - We’d like help with setting a “minimum bar” that antibodies would need to achieve to enter the Phase II-III Bayesian adaptive progressive trial that we’d be putting them through for ACTIV.

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group Working Group Meeting, Key Takeaways

Tuesday, May 19th, 2020

- At the moment, ACTIV doesn't need to prioritize necessarily but rather, goal is to identify minimum bar

Responses from Agent Prioritization Subgroup

- Suggestion to commission small expert team made up of people that Working Group members have access to and ask them to make a recommendation on how to assess and prioritize the agents given the deep technical issues involved.
- Agreement. Suggestion to bring people from networks that we're working with.
- At Roche, this work is done by experts. In agreement to have group of dedicated experts.
- Potential questions to pose to the super experts in mAbs:
 - What are the attributes for which we want on each of the antibody candidates?
 - What should be the minimum criteria that we'd apply in advancing candidates into clinical trials?
 - Strategic considerations – their advice on how important to target a variety of epitopes, or are there other viral proteins, are the effector functions desirable or undesirable, should we try to ensure we get a wide variety of antibodies, etc.
- Suggestion to look for experts with bioproduct development expertise
- 6-8 people

Other updates from Stacey Adam

- Landscape trackers – BARDA and Hever: we are continuing to work to get access to BARDA. We'll have an update from Hever tomorrow.
- RFI survey updates – we are in the process of putting everything into a REDCAP form. Data will be captured on an online form that companies will be able to access via a link. It will have drop down menus for certain sections, limited text populations, and appending of documents.
 - Suggestion from Working Group Members for two-staged process
 - Suggestion to distinguish the questions that must be answered vs. optional questions

Wave 2 process moving forward

- Similar process as before
- Note that we've also gotten submissions from investigators, academics, etc.
 - Send these contacts link to survey

Chatbox

From Peter.Stein to Everyone: 01:23 PM

I was just going to note that FDA has been giving companies consistent input on requirements for getting into the clinic and transition to Phase 2 (tox, in vitro assays, etc.)

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting, Key Takeaways

Tuesday, May 19th, 2020

From Stacey Adam to Everyone: 01:23 PM

Great!

From Carl's Lilly iPad to Everyone: 01:36 PM

Stacey - Did you say you had a list of the SARS-Cov2 antibody programs? If you do not, I can share what I pulled from the public domain. 38 programs.

From Peter Wung to Everyone: 01:51 PM

I apologize if this has been brought up or discussed before, but is there the possibility of using an AI platform in looking at pathways and drug targets to help add a separate "voice" in prioritizing these molecules for the next wave?

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group
Outpatient mAbs Writing Team Meeting #1, Key Takeaways

Monday, May 18th, 2020

Action Items

Action Items		
	Information	POC
1	Begin drafting statistical synopsis	Karen Price and Lisa LaVange
2	Share virology data from Lilly [to understand if a quantitative virologic assay can be used]	Ajay Nirula and Paul Klekotka
3	Set up a team to focus on minimal criteria to enter into Phase 2	Sarah Read, Eric Hughes, and Stacey Adam
4	Share synopsis and RFI with the CEOs of the 21 companies	Sarah Read, Eric Hughes, and Stacey Adam
5	Determine who should “own” or hold the protocol document	Stacey Adam
6	Schedule next call	Stacey Adam

Notes

- Introductions
- Question on moving forward, who should “own” or hold the document? Stacey to circle back, but likely needs to be the new statistical group additions for tonight.
- Karen Price: A lot of times, converting to Bayesian master protocol can increase efficiency and help manage greater size. Would like to discuss:
 - Questions about the structure of the document, what elements would be master protocol governed and elements up to an individual asset that comes in as far as sample size, allowance for additional dose arms in phase 2 for example (single dose / flexibility to allow for multiple doses), flexibility at asset level to help accommodate multiple assets coming in (especially if we can facilitate more borrowing as we go)
 - Questions about specifics of the endpoints
 - Structure of the document
- Joseph Eron: Is there a triaging of assets before entering phase 2 of trial?
- Stacey Adam: Yes, there will be a bar. This will be a parallel effort. There will be an outpatient and inpatient protocol. We envision that there will be a minimal bar that has to be met for an agent to proceed into the master protocols. Minimally, there has to be tox, early phase 1, etc. We want to make sure we are putting things that are safe for patients into a trial. The phase 2 will also try to screen things out rapidly. Also, not all companies will be ready at once. In the next few months, only 3-4 of the drugs will be ready.
- Joseph Eron: Are there in vitro characteristics of the antibody that will help with selecting?

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group Outpatient mAbs Writing Team Meeting #1, Key Takeaways

Monday, May 18th, 2020

- Sarah Read: Yes, the intention is that we will create that minimum bar, but it has not yet been thought of. Suggestion to set up a team to focus on minimal criteria to enter into phase 2.
- Judy Currier: Operationally, would that task fall under ACTIV or under this team?
- Sarah Read: It could be a combination, joint effort.
- Stacey Adam: Janet Woodcock is meeting with the CEOs of the 21 companies. They may weigh in on the minimal bar and assays.
- Karen Price: What level of flexibility would there be at the asset level? If written as an appendix, it can give more flexibility on things like number of patients. As we learn more, subsequent assets don't need as large of a sample size because we're utilizing some of the historical information.
- Sandeep Menon: Suggestion to be thoughtful about triaging early but also think about translational/early clinical stage where we get the best 10 to begin with. Many of them may have a similar mechanism and grouped together.
- Stacey Adam: Assume that we will have antibodies that target the same epitopes, but whether all of them come up simultaneously in the timeline is doubtful. Not sure, but it may be challenging.
- Ajay Nirula: The majority of the early antibodies are targeting receptive binding domain, but there are different epitopes within that. So, some of the triaging is important. There are some effective antibodies with effector function, without effector function, cocktails of antibodies, and some NTD-binding antibodies coming along. There will be a lot of options. Particularly, this protocol is well suited to test some of the cocktails.
 - At some point, would be interesting to discuss if we'd allow a few doses of antibodies. Defining ballpark in terms of dosing would be helpful.
- Michael Hughes: Biggest challenge in thinking about number of agents is how you triage which agents to take through to Phase 3 and how you efficiently allow discontinuation of agents that are faring less well in Phase 3 compared with other agents. That's potentially where a lot of the Bayesian decision rules can be productively used.
- Karen Price: Agree. We could map out specific interim analyses and the associated timing. For some of these, we could trigger the Phase 3, start off with smaller sample size and re-estimate to higher if the event rate isn't where it needs to be. One of the biggest concerns for me is the event rate for Phase 3 hospitalization, death, and ER visits.
- Michael Hughes: Conceptually in Phase 3, we need to decide whether it's really an agent vs. placebo or it's agent X vs agent Y. If you're talking about 21 agents at Phase 2, it wouldn't be inconceivable to have perhaps 5-6 agents move to Phase 3, which would be very large trial.
- Joseph Eron: Can phase 2 sort between agents, or will it just be plus/minus? As the protocol is written now, one of the primary endpoints for Phase 2 is the symptom score, time to resolution, or consistent improvement. It's hard to imagine that you'll be able to say agent A is better than B based on subtle differences in symptoms because it will be hard to control for the baseline population with smaller sample. What we'll learn quickly with the first agents, and with dose ranging, is whether virology will help us or not. If we figure out a scheme to collect virus shedding samples in a way that results in some minimization of variance within the individual; the sample

Monday, May 18th, 2020

size will shrink; we'll be able to distinguish between variance, maybe even see selection of resistance which would be a decision maker for single vs. dual. Virology aspect can be a much bigger sorter of activity if we can measure it and if correlated.

- Jonathan Li: There's some data from the COVID and other viral studies that you can see changes/early changes especially in viral loads with some of these antiviral agents. Ideally, if we have early virology data, could help potentially separate these agents. We're waiting for NIAID data.
- Judy Currier: We need to grapple with primary endpoint for Phase 2. Would be great to hear input from ACTIV, especially with FDA members on the call.
- John Farley: There have been some discussions about this in the FDA, but we're in very early stages in conversation with sponsors. Most sponsors are looking at the ordinal scales for these types of studies and either a one or two-point improvement. We're mostly focused in Phase 2A space, rather than Phase 2B which would be registrational. We need to learn from Phase 2A what a reasonable endpoint might be. What we're proposing looks fairly good for a start. The question is if it could be modified at the front end if it doesn't perform.
- Joseph Eron: This is Phase 2A. There's nothing in terms of activity that we will see before this.
- John Farley: I interpreted the question as what we're looking for in terms of substantial evidence for efficacy, which will be further on down the road. We haven't talked about endpoint at which one would stop.
- Davey Smith: Want to be careful that we don't really know if the symptom/virologic improvement is predictive.
- Stacey Adam: The idea is to have the two protocols harmonized as possible and as paralleled as possible between the outpatient and the inpatient because we will test same agents in both.
- John Farley: Also possible that an agent not successful in treatment can be successful in prevention. We don't have clear evidence of benefit concept in terms of the bar to move into prevention. We're seeing these as getting started primarily based on safety.
- Karen Price: May be worth talking about the symptom score – how we define success.
- Davey Smith: At the moment, people can start in mild, go to moderate, and go back to mild – we should capture that in our protocol for the primary and especially on the secondary endpoint for looking at progression.
- Michael Hughes: To some extent, it's tied into the population you allow to be involved. One of the things that we struggled with in trying to think through how to evaluate symptoms as an outcome measure is the possibility that you're enrolling participants for whom all of the symptoms are mild at study entry, and perhaps the increasing likelihood that as testing gets better, that will be a more significant part of your population. If people are having more mod or severe symptoms at entry, it's perhaps easier to think about definitions. The standard definitions in many flu studies was "resolution to all targeted symptoms to mild or absent." Really focused on getting rid of moderate or severe symptoms. But that endpoint doesn't work so well if a large proportion of your study population is coming in with mild, and they never progress. So, the two things are interlinked -

Monday, May 18th, 2020

study population/severity of symptoms of entry and the choice of outcome measure are interlinked.

- Joseph Eron: Clinically, COVID-19 has a 5-8 day ramp up, whereas influenza tends to be at its severest within a day. The other advantage is that the less symptomatic someone is, the higher their viral load is. You may lose clinical endpoint but potentially gain virologic endpoint. That's why having 2 endpoints may make sense.
- Michael Hughes: Agreed. May take several days for symptoms to ramp up, may be exactly when we're catching people.
- Stacey: We need to submit a synopsis by EOD Wednesday, 5/20. Should include:
 - What will we do for stats design – Bayesian for Phase 2
 - What need to pull together that isn't in protocol now:
 - Entry criteria – minimal bar threshold (studies by which this is measured)
 - Metrics of success, people getting better – ordinal scale? Modification of current ordinal scale? Something else?
 - Endpoint – symptomatic or virologic
 - What is the transition point, and how do we do that seamlessly from Phase 2 Bayesian design to Phase 3?
- Michael Proschan: Would be happy with a Bayesian design for Phase 2. May argue with some things he's heard earlier in the conversation if it's to be applied in Phase 3 (i.e. borrowing information from controls earlier in the trial – would be problematic for Phase 3)
- Joseph Eron: In terms of Phase 2, in this synopsis, it sounds like there's agreement that both virologic and symptom index makes sense to sort between agents that will have some bar when they come in. For the virology, our team has gone back and forth on whether there should be a virologic endpoint. Agreement that there should be two primary endpoints – one virology, one symptom-based?
- Stacey Adam: Up to the experts in the group. Don't disagree with 2 endpoints. Lilly will donate testing kits but not sure if that's for a re-test if that was an intention. It's a big decision that this group should make. If both virologic and symptomatic make sense, that's fine. We will probably need to put some suggestion of what we think the virologic could be, even if that changes as we learn more.
- Michael Proschan: Are you proposing that it would have to be both endpoints to move forward, or at least one?
- Joseph Eron: At least one because we were a little uncertain about whether virology would distinguish or not. Ideally, we would have some sort of triage where an agent that affects both would have some priority.
- Sandeep Menon: when we say virology endpoint, is it the viral load? IgG, IgM? What are we trying to measure here? Based on the patient population, are these endpoints used as core primary endpoint? Correlated or not? How do we use?

Monday, May 18th, 2020

- Davey Smith: Virology. IgG and IgM will be measured but not endpoint. Related to viral load. Your point about correlation is a good one. We would hope that if you decrease the virus you'd get better symptoms, and the two would go together, and that would help us more with our endpoint.
- Joseph Eron: The idea is that the outcome would be RNA shedding from the nasal pharynx. Currently, the way it's written, quantitative data is a secondary endpoint. Should we elevate it?
- Jonathan Li: Having quant would be phenomenal, but as of now, there's not one well-established quantitative assay that's commercially or EUA available right now. Would probably still defer to a qualitative, yes/no assay. If you look at a time to negative shedding by nasal pharyngeal swab, there is some precedent that that could be detectable.
- Karen Price: We've looked at some simulations evaluating AUC as well as change, say at day 11, or the time to clearance, and it's more powerful with the first two vs. a time to clearance approach. Not sure if an option is to have as the primary something quantitative with a supporting secondary as time to. We would lose quite a bit of power. You could see it, but it's definitely less powerful.
- Davey Smith: That's the big question on how we want to move things back and forth – one's primary now and one's secondary later. To John's point, we'll do all virology in central lab, so hopefully they'll be reliable. It's all about the inaccuracy, but that should help a lot.
- Ajay Nirula: As we move into smaller groups, we can share analyses. We've tested 50,000 people in Indiana. We have a lot of PCR data.
- Judy Currier: Are there large structural issues in overall design? How should we move forward with getting input quickly?
- Stacey Adam: Suggests that Karen take a stab at what adapting Phase 2 Bayesian would look like, and implications
- Karen: Yes, can do this. And can work with endpoints, dose levels to propose. Take schema from the current protocol.
- Peter Kim: Is the purpose of this trial to come up with the one best combination of antibodies that will work with outpatient treatment, or is the purpose to come up with a portfolio of various antibodies that will be available to use for treatment?
- Sarah Read: To come up with, as quickly as possible, one or more treatments. Doesn't need to be the best. As antibodies come along, if they're effective (however we define "effective"), then Janet Woodcock wants us to talk with manufacturers of about ramping up.
- Stacey Adam: If we start to find antibodies that were successful in their own right, Janet Woodcock would also want to speak with companies about combinations across companies coming up with ideal combination eventually, but this is not the short-term goal.
- Michael Hughes: In Phase 3, it would suggest you'd want to have some response adaptive randomization or dropping arms.
- Michael Proschan: would argue vehemently against response adaptive randomization. Dropping arms is fine. Response adaptive randomization has number of disadvantages.

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group

Outpatient mAbs Writing Team Meeting #1, Key Takeaways

Monday, May 18th, 2020

- Michael Hughes: Agree. But dropping arms because [of what reason]? It's a fundamental question that will be relevant to companies. Dropping arms because they're not doing well against placebo? Particularly well? Not doing as good by a long way as an alternative agent?
- Stacey Adam: In the short-term, it has to be better than SoC/baseline. It doesn't have to be better than everything else out there.
- Michael Hughes: That means in Phase 3, you'll continue multiple agents for longer periods because you won't be willing to drop arms that aren't performing as well as the best agents.
- Sandeep Menon: We'll need to move a little more adaptive in our decision making. Currently, we have an SoC and everything need to be compared to current SoC. When we get into Phase 3, we need to figure out what are the diff arms that survive. Revisit decision criteria. Will be a dynamic process.
- Michael Hughes: Can see a few of these assets crossing the bar at end of Phase 2. Will we then triage them for continuation in Phase 3? Or do that during Phase 3? Or will we just continue 6, 10, etc. products in Phase 3 and only drop those that aren't doing so well relative to placebo? Issue is the sheer scale of Phase 3 testing if lots of products move on to Phase 2.
- Next steps:
 - Karen Price and Lisa LaVange to tackle statistical synopsis
 - Need virologic/symptomatic endpoint refinement. Karen to share some of what they've done at Lilly
 - Share virology data that Lilly (Ajay and Paul) to understand if a quantitative assay can be used
 - Schedule next call

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group Working Group Meeting, Key Takeaways

Friday, May 15th, 2020

Action Items

Action Items		
	Information	POC
1	ACTT-3/ACTIV-1 subgroup to continue writing protocol	Working Group Members
2	David Goff to share draft of monoclonal antibodies protocol (outpatients)	David Goff
3	Monoclonal antibody subgroup to meet on Saturday, 5/16	Working Group Members

Key Takeaways

- Overview of ACTT-3/ACTIV-1 design decisions, and Working Group to move forward in drafting
- Regarding monoclonal antibody protocol: full Working Group did not reach a decision regarding ACTG protocol and involvement. A vote will be taken via email.
- Monoclonal antibody subgroup, including industry leaders, will meet tomorrow, Saturday 5/16 to sketch out (1) vision for monoclonal antibody protocols and (2) brainstorm the list of things that the monoclonal antibody protocol would need from a network.

Notes

- Review of ACTT-3/ACTIV-1 Design Principles, Design Details, Sample Size (see slides)
 - (b) (4)
 - Decision on moderate futility, 3 looks, stopping at 1.04 at the second look (stopping almost at the null)
 - Cumulative probability of taking bad drug forward is not even 1% at 75% of the way through; we're bounded by 15% futility at 85% power.
 - Have 4% chance at the second look at dropping something effective. This is moderately aggressive.
 - Don't have an accrual model; may not need at this time
- If group in agreement, will move forward with these assumptions and decisions in writing ACTT-3/ACTIV-1
- Feedback and questions from Working Group members:
 - If one of the drugs stops early for efficacy, will we change to offer that drug as SoC?
 - Depends on whether you think it's ethically feasible to continue
 - Will matter how rapidly we're enrolling. If we're enrolling rapidly, will be a moot point. If not rapid enrollment, we may have time to think about it.

Friday, May 15th, 2020

- All the recoveries would be included in even a DSMB interim analysis.
- Will the DSMB declare a winner or not? Companies worried that they will be left in limbo. Can we build something in where there's a discussion with the regulatory agency/steering committee before winner declared?
- If we're going forward with the monoclonal approach, should we focus on writing our monoclonal protocol instead of moving forward with and prioritizing ACTT-3/ACTIV-1?
 - DSMB as an independent body shouldn't consult steering committee before making a recommendation. They can't think from the company's perspective. They have to think about the safety of the participants.
 - From the public health perspective, the drug that DSMB approves should be able to be scaled.
- What happens if something does look good? Does it get added to SoC?
 - Needs further discussion, but do not think it should.
 - In the context of the drugs we are considering (immunomodulators, with all slightly different MOAs), makes sense not to add as SoC.
- Would there be an effect on enrollment if something came out to be very good, and it wasn't included in SoC?
 - Sense is that there will still be plenty of patients. We'll also be at a point where we won't have stopped the other drugs, so there's a chance that they will be effective as well.
- Regarding the Steering Committee
 - The sponsor for this study is ACTIV (the steering committee).
 - The steering committee makes the decision, not the DSMB.
 - The steering committee should look beyond just the results of this trial. There should be a discussion of what's good for all patients beyond just this trial before a decision is made.
 - In Ebola trial, DRC, DSMB felt like it was an ethical option to wait to see that a drug is really good. From a scientific perspective, want to know everything that's better than Remdesivir, but don't think that DSMB will think that way.
 - Steering committee should take into consideration the strength of the data.
 - Talking about what the steering committee will do may be premature.
- Time to move on to the monoclonal antibodies?
 - Co-Chair suggestion to put together smaller subgroup to move forward with ACTT-3/ACTIV-1
- Timeline with ACTT-3/ACTIV-1, from Stacey Adam:
 - Simulations conducted by Sandeep Menon and his team

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group Working Group Meeting, Key Takeaways

Friday, May 15th, 2020

- Working to get most recent ACTT-2 to make Remdesivir language the SoC in ACTT-3/ACTIV-1
- Aligning with the FDA
- Janssen is on board. We will work with them to get agent-specific sections populated.
- We're waiting to hear back from (b) (4) today. [Post Meeting Note: (b) (4) has committed to the protocol; we are working to get their agent specific info. (b) (4) has a few more questions for the team but is positively favorable; meeting with the team again Monday.]
- It should take about a week to complete first draft of ACTT-3/ACTIV-1; then send to FDA and companies for feedback. Uncertain about the review timelines
- Initial feedback from ACTT Team
 - No confirmation that we can add on ACTT-3/ACTIV-1
 - We updated them on our agent prioritization and where we are with protocol development.
 - They just started ACTT-2, concerned about competition for enrollment at their sites, asked for a few weeks to decide
 - Co-Chair sense is that we can't wait that long, and we should talk to other networks/CROs to see if they can take this on faster.
 - Good lesson for monoclonal antibodies. The protocol is the protocol. The network is separate.

Monoclonals

- We need to start moving on to monoclonal antibodies and to talk more closely with the Clinical Trial Capacity working group.
- 2 protocols will be developed in parallel (for monoclonal antibodies), hopefully starting at the same time (inpatient / outpatient).
 - Co-Chair: want to better understand what conversations companies have had with the FDA on what populations are best to pursue
 - Most companies are starting single ascending dose studies in hospitalized patients (moderate to some severe).
 - Most companies would then imagine doing their Phase II in mild ambulatory patients.
 - Third cohort is the prophylaxis cohort. There are currently discussions on how much data we would need.
 - Some companies might be running phase II trials in the moderate to severe patients in parallel; some companies are sequencing.

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group Working Group Meeting, Key Takeaways

Friday, May 15th, 2020

- David Goff shared knowledge of an existing draft of outpatient protocol (for monoclonals) within one of the NHLBI networks. Already shared with Mike Proschan (master protocol for open platform trial) and can share newer version.
 - Inpatient and Outpatient
 - SIREN and PRECISE for outpatient
 - PETAL, PTC, CTSN, heart failure network potential for inpatient
 - Groups that don't technically meet definitions of networks but have capabilities they're looking for (more like AROs, like DCRI)
- Monoclonal protocol should be more like a de novo. We will have to modify from ACTG and can't take as directly as we did from ACTT-2.
- We don't have to adopt protocols from networks that have come forward.
 - Would like to have a network/baseline home that will adopt our protocol, and then supplementing it with sites. That will be easier than going out and finding sites afterwards.
- Discomfort on voting for ACTG right now
 - Let's ask 3-4 of the biggest companies to share their protocol.
- ACTG is completely open to modifications from ACTIV. If they're selected as the "home" network, they'd like to be part of synthesizing it. The company that they worked with on monoclonal antibody was going to share what they sent to the FDA.
- Have we listened to UW protocol with Bill Gates? – Focus on Lozartin; not much hopes for this. Not adaptive
- Decision need to make about the network and sponsor – who will own it?
 - ACTG has expressed enthusiasm and flexibility and willingness to work with ACTIV, companies, etc. to develop the protocol in a way to suit ACTIV's needs.
 - Doesn't necessarily need to be ACTG alone. We could also work with other networks.
- If there are 21 monoclonals out there, operationally, we should think about what we need. We may not be the right people to make that judgement. Keith G. did 5-7 years of study with ACTG and doesn't think they have the resources we need. We don't want to be limited by sites, etc.
 - The issue of the network is important in terms of organizing (maybe ACTG can take administrative steps), but think we will need a few CROs, etc.
 - Agreement that the number of sites we were talking about is too small. If we're talking about 20+ drugs, we need more sites than what they're talking about now.
 - What they have is not a full protocol.
 - It's 75% complete. They're willing to send to ACTIV.
- Sub Chair: We could look at David's protocol, protocols from pharma (single protocol for ambulatory approach), I-SPY COVID (statistical analysis). We could craft protocol synopsis. These are not complicated master protocols. Think about Bayesian design for Phase II.

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group Working Group Meeting, Key Takeaways

Friday, May 15th, 2020

- Suggest that we brainstorm on protocol and get synopsis that we can send to the networks and give ACTG first shot.
- Tomorrow, monoclonal antibodies subgroup will discuss (1) vision for what monoclonal antibody protocol could look like, and (2) brainstorm the list of things that we need from a network. We need to turn this over to Clinical Trial Capacity Working Group by the end of the day tomorrow, 5/16.
 - Clinical Trials Capacity Working Group submitted a list of highest priority Tier 1 networks (based on when shovel ready, focused on and capable on in-patient space) to ACTIV leadership. ACTG was included on that list.
 - Shovel ready: networks that had at least told ACTIV that they can get 50% of sites up and running in 6 weeks, or 75% of sites up and running within 12 weeks; with standard contracting; comfortable with single IRBs
 - Any CRO can do this. That's why issue of the network shouldn't be our first issue.
 - Currently surveying CROs and SMOs to see about their capabilities
 - ACTG wants to be a leader in this, consistent with what clinical trial capacity group has recommended to ACTIV leadership.
- Recap
 - Group undecided on ACTG.
 - Monoclonal antibodies subgroup tomorrow will try to sketch what patient population will be.
 - We will have conversations with networks on their amenability to ACTIV writing the protocol for them. We will bring companies along.
 - By early next week, we should know who the early companies are.
 - Monoclonal antibodies summit still aimed for next week. Janet will have pre-summit with the 21 company CEOs.

Chatbox

From (b) (6) to Everyone: 01:22 PM

@Keith: I don't understand your comment around harm to public health...

I agree with Joan

From Eric Hughes to Everyone: 01:26 PM

I would not count on rapid enrollment.

From Keith Gottesdiener to Everyone: 01:27 PM

sorry, Sam. back to important stuff....

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group
Working Group Meeting, Key Takeaways

Friday, May 15th, 2020

From Libby Higgs to Everyone: 01:30 PM

Any initial feedback from ACTT Team? I had to drop off the call half way through

From Libby Higgs to Everyone: 01:45 PM

Sorry all I have to leave (for a GATES call) . I would support working w the ACTG as the network for the outpatient monoclonal protocol w the proviso that the design can be modified per group input.

From (b) (6) to Everyone: 01:48 PM

I also would be happy to work with the ACTG + others from what we know now but agree that we need to see the draft protocol

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) Co-Chairs briefed WG members on the previous day's ACTIV Executive Committee meeting, which was convened to discuss the TX-Clinical WG's letter identifying challenges that have impeded this WG's efforts and requesting specific Leadership Group activities to help resolve these challenges. Executive Committee members focused mainly on the TX-Clinical WG's proposal to start an ACTIV master protocol exclusively for testing all available SARS-CoV-2-specific monoclonal antibodies (mAbs) in head-to-head comparisons. The TX-Clinical WG discussed the outcomes from the Executive Committee meeting and strategized about next steps for launching its mAb master protocol.

The WG also briefly reviewed simulations conducted by Dr. (b) (4), (b) (6) team at (b) (4) to help inform boundaries for the ACTT-3/ACTIV-1 master protocol's interim efficacy and futility analyses.

ACTIV Executive Committee Meeting Debrief

During its meeting yesterday, the ACTIV Executive Committee discussed the TX-Clinical WG's letter identifying challenges and recommendations, focusing on three main topics: (1) launching an accelerated master protocol to test all candidate SARS-CoV-2-specific mAbs; (2) creating and maintaining a global landscape assessment of existing *and planned* efforts (publicly announced and those not shared publicly yet) to assess therapeutic agents for potential efficacy against COVID-19; and (3) aligning and communicating efforts more effectively across ACTIV partners and WGs. Dr. Francis Collins noted that the Hever Group and Accenture are currently mapping all ongoing and planned COVID-19 activities but have not yet been able to coordinate efforts or to eliminate redundancies. He also agreed that the ACTIV leadership group should connect the TX-Clinical WG with both the Hever Group and Boston Consulting Group so that the WG can assess the efforts and identify further needs.

The Executive Committee also briefly discussed the need for a (b) (4) Dr. Collins advocated for investigating platforms already developed by both (b) (4) COVID-19 (b) (4) to see if they could be adapted for use by ACTIV. Executive Committee members agreed to nominate members to form a new WG or Subgroup to explore challenges and possibilities around establishing a (b) (4) for ACTIV (e.g., to survey existing platforms and to determine what is specifically needed). Co-Chairs of other ACTIV WGs had the opportunity to request assistance from or provide feedback to the ACTIV Executive Committee.

Dr. Adam will clarify timelines for the action items from the Executive Committee meeting.

Executive Committee Discussion of the Monoclonal Antibodies Master Protocol

Most of the Executive Committee's discussion centered around the TX-Clinical WG's proposal to develop a master protocol exclusively to test SARS-CoV-2 mAbs. Executive Committee members strongly supported this proposal, highlighting the potential benefits of testing many candidate mAbs under a master trial design with uniform endpoints and a shared control arm. Dr. Janet

Woodcock of the Food and Drug Administration (FDA) confirmed that at least 21 companies have mAbs in development and that some of these companies plan to launch trials in mild-to-moderate and severe patient populations as soon as June 2020. Drs. Woodcock and Collins are working to organize an ACTIV-sponsored summit next week of all known companies developing SARS-Co-V-2 mAbs. During this summit, ACTIV leadership will gauge companies' willingness to enter their mAbs into a master protocol for head-to-head comparisons and will ask the companies to provide fuller information on their mAbs (FNIH is developing a form to solicit all data of interest).

Dr. Woodcock strongly recommended drafting two separate mAb master protocols—one for inpatients and one for outpatients. Executive Committee members stressed that many NIH Institutes and Centers possess master protocols that could be adapted for ACTIV's mAb master protocol. Dr. Woodcock also listed several operational issues that the TX-Clinical WG should work to resolve as quickly as possible:

- Who will serve as the Principal Investigator (PI)?
- Where will the Data Coordinating Center be located and who will manage it?
- What entity will be responsible for setting up the sites to execute the protocol?
- Might companies' mAbs that enter trials before ACTIV's master protocol is established be retested later under ACTIV's master protocol for better comparability of trial data?
- What existing clinical trial networks, sites, and master protocols could be leveraged to rapidly design and execute these mAb trials?
 - These resources could include infrastructure controlled by NIH, BARDA, industry, contract research organizations (CROs), nonprofit foundations, and others. Dr. Woodcock noted that BARDA has contract agreements with three CROs that could help to fill gaps in the existing infrastructure landscape.
- Who will be responsible for writing/designing the mAb master protocol?

Participants also suggested leveraging the AIDS Clinical Trials Group (ACTG)'s master protocols to guide ACTIV's mAb master protocol design. ACTG has expressed a desire to join ACTIV's efforts and the ACTG PI, Dr. Judith Currier, is an ACTIV member who could potentially serve as the PI for ACTIV's mAb master protocols. ACTG's existing master protocols are agnostic to agent class, although they currently focus on moderately ill patients.

The Executive Committee proposed that the TX-Clinical WG draft the mAb master protocol within the next 2 weeks.

TX-Clinical WG Discussion of the Monoclonal Antibodies Master Protocol

TX-Clinical WG members discussed whether to begin designing an mAb master protocol before securing buy-in from companies developing mAbs, or to secure company buy-in and gather all available information on their agents before drafting the protocol. Some members, including Drs. Keith Gottesdiener, John Mellors, and Timothy Buchman, favored the latter approach, and expressed skepticism regarding whether the ACTIV mAb summit next week will be sufficient to convince companies to submit their mAbs for ACTIV head-to-head testing. They suggested that

the Leadership Group should apply more direct pressure to the CEOs to encourage company participation.

Others disagreed, advocating for first developing a master protocol design to give companies a more concrete proposal to react to. Those advocating for the latter approach emphasized that companies will be willing to participate in ACTIV's mAb master protocols if their agents can be rapidly, robustly, and cost-effectively tested. Drs. Carl Garner and Sarah Read agreed that ACTIV Leadership Group members (e.g., Drs. Collins and Woodcock) should directly contact CEOs from ACTIV partner companies with SARS-CoV-2 mAbs in development to ask that they each commit an expert clinical staff member to help ACTIV design its mAb master protocol.

Dr. Peter Stein also suggested establishing an operational subgroup to specify all the design characteristics and operational details needed to launch this master protocol. It is crucial that representatives of the Clinical Trial Capacity WG be included in this subgroup so that group can begin organizing suitable networks and sites as quickly as possible.

ACTG and INSIGHT could be adapted for ACTIV's outpatient and inpatient mAb trials, respectively, although substantial changes may be needed. Dr. Stacey Adam highlighted that modifying ACTG and INSIGHT (e.g., supplementing with additional sites) may be preferable to starting fresh, because these existing networks have already secured buy-in from clinical trialists at specific sites, which is crucial to a trial's success. Dr. Judith Currier of ACTG confirmed that ACTG is willing to accommodate adjustments depending on what ACTIV needs to execute its mAb protocol. Participants also noted that the INSIGHT network (whose investigators will meet with the TX-Clinical co-chairs tomorrow) has sites that are already prepared for upcoming immunoglobulin trials, which could provide a 'shovel-ready' network for ACTIV's inpatient mAb trials.

Next Steps for Establishing Monoclonal Antibodies Master Protocol

Dr. Adam will connect with ACTIV leadership to ensure that they contact CEOs of partner companies developing SARS-CoV-2 mAbs and to clarify the timeline and plan for the summit next week. She will also discuss with the Master Protocol Subgroup tomorrow the possibility of adapting the ACTG and INSIGHT protocols and networks (with CRO support) for outpatient and inpatient mAb master protocols, respectively. TX-Clinical WG members will either volunteer themselves or nominate individuals from their respective organizations to join a Monoclonal Antibody Master Protocol Subgroup, and Dr. Adam will schedule that subgroup's first meeting for this Saturday, May 16. Dr. Adam will also ensure that this subgroup contains experts from all domains necessary to fulfill its remit.

Boundaries for ACTT-3/ACTIV-1 Interim Futility and Efficacy Analyses

Dr. (b) (4), (b) team at (b) (4) has used (b) (4)

(b) (4) The idealized model assumed (b) (4)

(b) (4)



The Master Protocol Subgroup reviewed these scenarios and favored the 'three-stopping-points' scenario paired with 'moderately aggressive' criteria to drop a drug for futility or lack of efficacy. Under this scenario, three interim analyses would occur (i.e., at the points when 25, 50, and 75 percent of desired information had been gathered) and criteria to drop a drug for futility or lack of efficacy would become less stringent from one stopping point to the next (i.e., the more information is gathered, the higher-performing the drug must be to continue testing).

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Medical Corps, US Navy*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Yuan-Li Shen, *Deputy Director (Acting), Division of Biometrics V, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer, NIH*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Sandeep Menon: 12:10

Can we collaborate with the COVID R&D for data sharing

Stacey Adam: 12:27

We can discuss.

Ruxandra Draghia-Akli: 13:28

and with (b) (4) -they already started

Sandeep Menon: 14:07

I think (b) (4) is already a part of (b) (4) sharing initiative, but not sure

Keith Gottesdiener: 17:33

they are collaborating (b) (4)

High-Level Meeting Summary

The Agent Prioritization Committee (APC) of the Clinical Therapeutics Working Group (TX-Clinical WG) adjusted and finalized agent scoring criteria in preparation for a second agent prioritization wave. Members also provided initial feedback on a draft Request for Information (RFI) whose results will be incorporated into the scoring process. Members also continued their discussion of whether to facilitate a trial of a particular (b) (4) and considered what kind of tracking system would enable such decisions.

A summary of key discussion points follows.

Criteria Scoring

The APC reviewed the overarching framework for its second wave of agent prioritization and adjusted weights and no-go criteria in both stages of its envisioned scoring process.

Stage 1 Scoring: Effectiveness

Stage 1 scoring applies four criteria: (1) rationale for Mechanism of Action (MOA) in SARS-CoV-2 treatment; (2) PK/PD; and experimental data, divided into (3) preclinical data and (4) clinical data. MOA rationale is the most heavily weighted criteria, whereas PK/PD receives less weight. Experimental data is weighted differently according to agent class, with preclinical data emphasized for antivirals and clinical data emphasized for immunomodulators. Participants discussed considerations for several of these scoring criteria.

- **MOA:** Drs. Michael Vincent and Sarah Read noted the weighting of MOA rationale might lead to exclusion of poorly understood agents that may nevertheless be effective. Although participants retained current weighting to reflect the importance of understanding *how* agents work, they agreed that the APC will revisit agents whose rationale for MOA is weak but whose experimental data are strong. Dr. Vincent added that reviewers will need to distinguish an uncertain MOA from a weak rationale.
- **Preclinical Data for Immunomodulators:** The APC agreed to eliminate a no-go measure from its preclinical scoring rubric. Using that measure would risk eliminating agents even after they showed promise in high-quality clinical trials. Participants acknowledged that preclinical data might reveal no-go *safety* issues but agreed that those issues will be separately addressed during Stage 2 of the scoring process.
- **PK/PD:** Participants reconsidered whether insufficient PK/PD data should constitute a no-go in the PK/PD scoring rubric or if that standard would lead to elimination of potentially valuable agents. However, following Dr. John Mellors' suggestion, they agreed that insufficient data would preclude a clinical trial—the goal of the prioritization process—and thus should be reserved as a no-go measure. The APC agreed that RFIs will help ensure that all available data are represented in the scoring process.

Stage 2 Scoring: Limitations

Stage 2 scoring applies three criteria: (1) safety, (2) drug/drug interactions, and (3) availability/scalability, each of which has a no-go measure as well as a numerical rubric.

Participants discussed considerations for each of these scoring criteria.

- **Safety:** Dr. Vincent noted that certain safety calculations change based on disease progression, and thus that certain safety concerns might be integrated into an MOA assessment rather than incorporated into the binary “safe” or “unsafe” distinction applied during Stage 2. Participants generally agreed and noted that Dr. Stacey Adam has created documentation to help reviewers understand and apply these conventions during the scoring process.
- **Drug/Drug Interactions:** Based on Dr. Keith Gottesdiener’s observation that all agents exhibit *some* drug interactions, the APC adjusted a score of “0” to reflect no *significant* interactions.
- **Availability/Scalability:** Participants discussed whether to move availability/scalability from scoring and instead to employ it as a last-step filter on scored agents. However, Dr. Gottesdiener noted that this criterion may be the most likely cause for removing agents from consideration and thus should be reflected in scoring. Participants agreed to retain the criterion and emphasized the importance of collecting multiple forms of data to inform scores. While RFIs will provide related data, APC members may also draw on their expertise to assess the validity of responses.

Data Collection and Monitoring Efforts

During its May 12 meeting, the APC discussed the need to more effectively collect and monitor data relevant to its agent prioritization efforts. Members have expressed interest in developing a visualization of the overall landscape of studies related to COVID-19 as well as a survey to collect specific information about agents being considered. Participants discussed and provided feedback on both efforts.

Landscape Tracker

Dr. Adam noted that several COVID-19 trackers have been developed by other organizations. She presented a sample tracker from Oxford University, focusing specifically on **10b** studies, for consideration as either a stop-gap or ongoing resource for ACTIV. Participants generally agreed that although this sample provides useful orienting information (including trial phase, title, sponsor, and duration, as well as countries of operation), a robust tracker would require information on trial status, details on intended sample size, and fuller coverage of large trials. Dr. Adam noted that the team is still trying to get access to more complete data trackers through BARDA and Hever.

Request for Information

The APC has developed a draft RFI to collect drug data for the scoring process. Although the RFI will primarily be distributed to pharmaceutical companies, it will also be shared with individuals who nominate an agent of interest through the NIH’s public portal.

Similar to the scoring process, the RFI is sensitive to agent class: certain parts of the RFI will be completed for all agents whereas others will be completed for either antivirals or immunomodulators. Dr. Adam noted that the survey generally seeks to balance the need for

specific and thorough information with the need to reduce the burden on companies and thus increase the response rate. Participants emphasized that the use of drop-down menus to structure responses will assist in streamlining collection and collation of responses.

Participants agreed on several revisions to the RFI survey questions:

- The opening request for information about human indications will clarify that *any* indications are considered relevant, not only those related to COVID-19.
- Requests for clinical data will solicit type of study and patient population.
- Requests for clinical data will solicit details on patient population and type of study (e.g., case series, anecdote, etc.).
- Preclinical data will be clearly limited to SARS-CoV-2.
- References and/or links to published case studies will be solicited.
- PK/PD questions will solicit information about how drugs are cleared from the body.

Dr. Peter Stein notified the APC that the FDA has begun a similar data collection process and recommended that ACTIV ask the agency to solicit respondents' permission to share the results with ACTIV participants.

Request for Assistance in (b) (4) Trial

The APC reconsidered (b) (4) request for ACTIV to help support recruitment for a trial of its (b) (4) (b) (4). Participants agreed that this specific request is not technically formulated in terms of agent prioritization. However, as Drs. (b) (4), (b) (6) pointed out, the request raises the broader question of (b) (4) and if so, whether facilitating this request is the best way for the APC to facilitate that prioritization.

Dr. (b) (4), (b) (6) shared a summary of (b) (4) to help the APC answer this question. The summary revealed several large ongoing studies, one of which is scheduled to release results in late May. Given this landscape, Dr. (b) (4), (b) (6) argued that the APC should not devote precious prioritization resources to (b) (4) at this time (b) (4) request can be referred to the Clinical Trial Capacity Working Group, which can decide whether to share the request with sites, which can then decide whether to respond.

Dr. (b) (4), (b) (6) also noted that (b) (4) request exposes ongoing strategic challenges to efforts against COVID-19: the fact that a company is soliciting urgent assistance for an agent class that has several fairly robust trials underway underscores the urgent need for communication among researchers to facilitate effective allocation of resources and avoid duplication of efforts.

Next Steps

APC members will share any further RFI feedback with Dr. Adam; Dr. Buchman will also share with Dr. Adam ideas about how to adapt the RFI questions to collect information on supportive therapies (e.g., anticoagulants). Dr. Adam noted that as the APC moves into Wave 2

prioritization, the group's co-chairs are assessing sixty ideas submitted by individual investigators that may ultimately be considered by the full APC.

Dr. Adam also reported that ACTIV's negotiations with companies to enroll Wave 1 agents in ACTIV clinical trials will continue alongside Wave 2 agent prioritization; one of those negotiations has already secured a commitment.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomaterials Capital; Therapeutic Accelerator Lead, Gates Foundation*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

INVITED PARTICIPANTS

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

00:14:30 **Peter Wung:** Are we still taking the top 2-3 scored or do we need to have a quality score cut-off?

Accelerating COVID-19 Therapeutic Interventions and Vaccines

ACTIV Partnership Executive Committee Meeting

May 13, 2020, 8:00 – 9:00 am ET

May 13, 2020



This meeting summary was prepared by Lucas Smalldon, MA, Rose Li and Associates, Inc., under contract to the Foundation for the National Institutes of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH.

Action Items

Action	Owner
1. Plan and host a Summit, organized by ACTIV, during the week of May 17 to convene the (21) companies developing monoclonal antibody therapies for COVID19 to discuss the goal of committing to an ACTIV-sponsored master protocol	Janet Woodcock, FDA (FNIH to host)
2. Develop the list of required data to be requested at the Summit from companies interested in joining the MP effort	Preclinical and Therapeutics Clinical Working Groups
3. Design and establish one or more master protocols for monoclonal antibodies that address sick outpatient and sick inpatient populations and that can accommodate both current/near-term agents as well as later candidates. The plan needs to include appropriate protocol design(s), choice of networks and sites, preclinical assays, data management centers, etc.	Therapeutics Clinical Working Group
4. Ensure mapping of all proposed ACTIV protocols to appropriate NIH networks	Anthony Fauci, NIAID, and Gary Gibbons, NHLBI
5. Reconnect with the (b) (4) to find out the status of (and accelerate if need be) their plans to do a landscape analysis of COVID-19 efforts and determine if there are gaps that need to be addressed.	Francis Collins and (b) (4), (b) (6)
6. The Preclinical working group will continue to work with the NPRC directors and ORIP to coordinate NHP testing needs.	Preclinical Working Groups
7. Executive Committee will consider providing a high-level message to CROs that have responded to ACTIV surveys to help inform them of next steps in assisting ACTIV	Clinical Trials Capacity Working Group
8. Executive Committee will assist in linking appropriate CDC personnel with the Vaccines WG to facilitate geographical mapping of COVID-19 attack rates	Vaccines Working Group
9. Consider further the request to establish a potential additional ACTIV workstream to create a centralized data warehouse/cloud infrastructure for sharing clinical trials and real-world evidence data on COVID; or whether simply to partner with other initiatives in this area	Francis Collins, Executive Committee, David Wholley

High-Level Meeting Summary

The Executive Committee of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership met with Co-Chairs of all four ACTIV Working Groups (WGs) to discuss how ACTIV's Leadership Group might assist the WGs in fulfilling their respective remits. In particular, the Executive Committee and WG Co-Chairs discussed a letter submitted to ACTIV's Leadership Group by the Therapeutics-Clinical (TX-Clinical) WG. This letter identified several challenges that have slowed or impeded the TX-Clinical WG's efforts and requested that the Leadership Group initiate specific activities to help resolve these challenges. Meeting participants discussed three main topics: (1) launching an accelerated master protocol to test all candidate SARS-CoV-2-specific monoclonal antibodies (mAbs); (2) creating and maintaining a global landscape assessment of existing *and planned* efforts (publicly announced and not) to assess therapeutic agents for potential efficacy against COVID-19; and (3) aligning and especially communicating efforts more effectively across ACTIV partners and WGs. Participants briefly discussed the need for a cloud-based data sharing platform, and Co-Chairs of other ACTIV WGs had the opportunity to request assistance from or provide feedback to the ACTIV Executive Committee.

Master Protocol for SARS-CoV-2-Specific Monoclonal Antibodies

The TX-Clinical WG's efforts to design a master protocol have thus far focused on three agent classes: (1) antivirals, (2) immunomodulators, and (3) supportive/symptomatic therapies (e.g., anticoagulants). However, TX-Clinical WG members, including partnering companies, have also expressed strong interest in developing a master protocol exclusively to test SARS-CoV-2 mAbs.

Several companies have mAbs in development, with the intent to begin trials in mild-to-moderate and severe patient populations during June 2020. TX-Clinical WG members think that a comprehensive overview of these existing mAb testing efforts (including those not yet publicly announced) is needed to assess the potential value and feasibility of an ACTIV SARS-CoV-2 mAb master protocol, and have proposed that the Leadership Group mobilize its connections and its resources both to provide this landscape overview and to encourage companies to submit their mAbs to ACTIV's master protocol where feasible.

Executive Committee members supported the idea of launching an ACTIV SARS-CoV-2 mAb master protocol, highlighting the potential benefits of testing many candidate mAbs under a master trial design with uniform endpoints and a shared control arm. Although some already planned industry mAb trials will begin before ACTIV's mAb master protocol can launch, ACTIV's master protocol *design*, once completed, could provide standardized endpoints that could still be added to previously planned studies to facilitate mAb testing data comparability.

ACTIV to Convene a Summit with Organizations Developing SARS-CoV-2 mAbs

Dr. Janet Woodcock of the Food and Drug Administration (FDA) confirmed that 21 companies are currently involved in developing SARS-CoV-2-specific mAbs, some of which have not been

publicly announced. Dr. Woodcock agreed to share the list of 21 companies with participants. She also noted potential concerns about manufacturing mAbs at scale but acknowledged that this challenge lies outside the scope of ACTIV's remit.

Following a proposal from Dr. Woodcock and Dr. Francis Collins, participants agreed that ACTIV will convene a separate summit **next week (between May 18-22)** among the 21 companies developing SARS-CoV-2-specific mAbs to learn about their current plans and gauge their willingness to align efforts and submit their candidate mAbs for testing under the envisioned ACTIV master protocol. Dr. Paul Stoffels highlighted that companies would generally be willing to join this effort if it facilitates robust, rapid, and cost-effective testing of their agents. During the summit, organizations will be asked to reveal more information about their current plans to develop and test mAbs than what has already been publicly revealed. FNIH will prepare a form to distribute to companies during the mAb summit soliciting data of interest.

Establishing Multiple ACTIV mAb Master Protocols

Participants agreed that ACTIV should develop multiple mAb master protocols, each targeting a different patient population. They stressed that various NIH Institutes and Centers—such as the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute (NHLBI)—have master protocol designs that could be quickly inventoried, assessed, and potentially adapted for ACTIV's mAb master protocols.

Operational Considerations for ACTIV's mAb Master Protocols

Dr. Woodcock listed several operational issues that need resolution before ACTIV can establish its SARS-CoV-2-specific mAb master protocols. She stressed that the main operational challenge will be to identify suitable clinical sites, map them against the geography of COVID-19 outbreaks, and enroll enough patients (likely with contract research organization [CRO] support) to execute adequately powered studies. She also identified more specific questions:

- Who will serve as the Principal Investigator (PI)?
- Where will the Data Coordinating Center be located and who will manage it?
- What entity will be responsible for setting up the sites to execute the protocol?
- Might companies' mAbs that enter trials before ACTIV's master protocol is established be retested later under ACTIV's master protocol for better comparability of trial data?
- What existing clinical trial networks, sites, and master protocols could be leveraged to rapidly design and execute these mAb trials?
 - These resources could include infrastructure controlled by NIH, BARDA, industry, CROs, nonprofit foundations, and others. Dr. Woodcock noted that BARDA has contract agreements with three CROs that could help to fill gaps in the existing infrastructure landscape.
- Who will be responsible for writing/designing the mAb master protocol?

Drs. Sarah Read and Eric Hughes, Co-Chairs of the TX-Clinical WG, agreed that their WG would work to address these questions during the next 48 hours.

Dr. Woodcock anticipates being able to help resolve some of the key operational issues, leaving ACTIV to focus primarily on core scientific questions. Simple master protocol designs will help ease challenges. Participants also suggested potentially leveraging the AIDS Clinical Trials Group (ACTG)'s master protocols to guide ACTIV's mAb master protocol design. ACTG has expressed a desire to join ACTIV's efforts and the ACTG PI, Dr. Judith Currier, is an ACTIV member who could potentially serve as the PI for its mAb master protocols. ACTG's existing master protocols are agnostic to agent class, although they currently focus on a mild to moderately ill outpatient populations.

Dr. Woodcock also noted that existing randomized controlled trials (RCTs) testing convalescent plasma in recovering patients may provide valuable proof-of-principle (PoP) data to help inform ACTIV's efforts.

Scientific and Policy Considerations for ACTIV's mAb Master Protocols

In addition to the operational considerations listed in the previous section, Dr. Woodcock noted several key scientific and policy considerations requiring decisions before launching ACTIV mAb master protocols: (1) What level of treatment effect/power calculations are needed? (2) What patient populations will be studied (Dr. Woodcock recommends designing separate protocols for inpatients and outpatients); (3) What endpoints will be measured? (Dr. Woodcock mentioned '[avoidance of] hospitalization' as one example of a potential outcome measure among outpatients).

Global Landscape of Existing and Planned Efforts Against COVID-19, and Communicating and Aligning Efforts Among ACTIV Partners and WGs

The TX-Clinical WG's letter to the ACTIV Leadership Group reported that the WG's capability to make strategic decisions has been impeded by its lack of knowledge regarding what non-ACTIV efforts exist to develop, prioritize, and test agents against COVID-19 (including efforts by some ACTIV partner organizations that either preceded ACTIV or are being executed in parallel). The TX-Clinical WG needs the capability to assess in real time how many agents of a given class are being tested and in what patient populations; using what trial designs, outcome measures, and sample sizes; and with results expected in what timeframe.

The TX-Clinical WG stressed that it needs to understand activities undertaken by ACTIV partners and other ACTIV WGs, not only external efforts. Drs. Read and Hughes stressed that *communication* is the primary issue, not a desire to integrate all such activities under the ACTIV umbrella. Without fully understanding the current landscape, ACTIV WGs cannot intelligently allocate their resources to fill gaps in that landscape or harmonize efforts with other activities. Therefore, the TX-Clinical WG has requested that the ACTIV Leadership Group provide WGs with a comprehensive catalogue of all COVID-19 efforts being undertaken by ACTIV partners in government and industry. Dr. Collins informed participants that the Hever Group and Accenture had reported their intention to map all ongoing and planned COVID-19 activities with a view to

identifying redundant efforts but have not yet communicated their progress on that score. David Wholley noted that the Hever Group's landscape mapping has not advanced quickly and suggested that members of ACTIV's Executive Committee (e.g., Dr. (b) (4), (b) (6) from (b) (4) and Dr. (b) (4), (b) (6) of (b) (4) might be able to help accelerate their efforts. Dr. Collins also proposed that TX-Clinical WG members review the (b) (4) information solicitation to ensure that it asks all questions that the WG needs answered.

Dr. Read noted that members of the TX-Clinical WG reported yesterday that (b) (4) is also currently compiling a similar COVID-19 activities landscape for the Assistant Secretary for Preparedness and Response (ASPR). Dr. Woodcock confirmed (b) (4) involvement with ASPR and noted that (b) (4) is also working with the (b) (4). Moreover, Dr. Woodcock has been compiling a separate inventory of ongoing COVID-19 clinical trial efforts using clinicaltrials.gov and the World Health Organization (WHO). Currently, (b) (4)

Dr. Woodcock will share the updated inventory with ACTIV participants, and the ACTIV Executive Committee will connect the (b) (4) with the TX-Clinical WG in order to assess their efforts and identify further needs.

Need for a Cloud-Based Data Sharing Platform

The TX-Clinical WG's recommendations to the ACTIV Leadership Group included a proposal for ACTIV to develop data sharing agreements and a cloud-based data sharing infrastructure that would allow real-time circulation of study documents and clinical trial results. Participants agreed that data sharing will be of crucial importance. Dr. Collins advocated for investigating platforms already developed by both (b) (4) COVID-19 Therapeutics Accelerator to see if they could potentially be adapted for use by ACTIV. Executive Committee members agreed to consider establishing a new WG or Subgroup to explore challenges and possibilities around establishing a data sharing platform for ACTIV (e.g., to survey existing platforms and to determine what is specifically needed). Any such data sharing platform must be fully functional across both government and industry.

Input from Other ACTIV WG Co-Chairs

To conclude the meeting, Dr. Collins invited Co-Chairs of ACTIV's other WGs to provide additional input.

Therapeutics-Preclinical WG

Dr. John Young raised the issue of prioritizing among competing requests to use nonhuman primate (NHP) resources for testing candidate agents. The TX-Preclinical WG is collaborating with National Primate Research Center (NPRC) Directors to establish an NHP prioritization process, yet the WG remains unsure of how this process will be coordinated with NIH Institutes. Institutes are currently receiving requests from researchers to conduct NHP studies, but NPRCs have agreed to halt NHP studies until ACTIV has prioritized therapeutics for testing. TX-Preclinical WG members have raised concerns about potentially impeding other COVID-19

preclinical testing activities that are set to begin. Dr. Young noted that the NPRCs may benefit from a central coordinating center to receive and assess study requests. The Preclinical working group will continue to work with the NPRC directors and ORIP to coordinate NHP testing needs.

Clinical Trial Capacity WG

Dr. Michael Kurilla stressed that the Clinical Trial Capacity (CTC) WG has completed most of its work on inventorying existing capacity and now needs to begin liaising more directly not only with the various ACTIV WGs and Subgroups, but also with the clinical trialists across NIH's and other networks to assess their experience and capabilities in more detail (e.g., experience with remote site activation and monitoring, electronic medical record linkage). This follow-up is needed before executing ACTIV's master protocol trials. Ms. Elizabeth Desrosiers also suggested that the Executive Committee provide a high-level message to CROs that have responded to ACTIV surveys to help inform them of next steps in assisting ACTIV. Dr. Collins suggested that this issue be discussed further offline.

Vaccines WG

Dr. Kathrin Jansen noted that the Vaccines WG would benefit from connecting with Centers for Disease Control and Prevention (CDC) groups assessing COVID-19 attack rates in different parts of the U.S. population (and elsewhere). This information will help to ensure sufficient statistical power for the Vaccines WG's harmonized phase III vaccine protocols. The Executive Committee can assist in linking appropriate CDC personnel with the Vaccines WG to facilitate geographical mapping of COVID-19 attack rates.

JAMA Publication

Dr. Collins concluded the meeting by noting that he and Dr. Stoffels have co-authored an article to be published soon in the *Journal of the American Medical Association*, which presents ACTIV and explains its goals. ACTIV representatives can use this article as a common reference to help convey the effort's aims and activities.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader; Executive Committee Co-Chair)*

Christopher P. Austin, MD, *Director, NCATS, NIH*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Anthony S. Fauci, MD, *Director, NIAID, NIH*

Maria Freire, PhD, *President and Executive Director, FNIH*

Gary H. Gibbons, MD, *Director, NHLBI, NIH*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson (Executive Committee Co-Chair)*

Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*

Carrie Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

Stacey Adam, PhD, *Director Cancer, Foundation for the NIH (FNIH)*

Cheryl Melencio, *Administrative Manager, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, *Consultant, Deloitte*

Margaret Anderson, *Managing Director, Deloitte*

Olivia Elsaid, *Consultant, Deloitte*

Nina Gonzalez, *Senior Manager, Deloitte*

Elizabeth Kim, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Jonathan Wachtel, *Manager, Deloitte*

Lucas Smalldon, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting, Key Takeaways

Thursday, May 14th, 2020

Action Items

Action Items		
	Information	POC
1	Send revised criteria scoring guide	Stacey Adam / Elizabeth Kim
2	Share request regarding (b) (4) request with Clinical Trials Capacity Working Group for follow up	Stacey Adam
3	Suggestions re: immunomodulatory agents	Timothy Buchman / Stacey Adam

Key Takeaways

- Key Criteria Scoring Post Triage: Stage 1
 - Antivirals: criteria scoring updates – no further changes needed at this time
 - Immunomodulators: criteria scoring updates
 - If there are data from one or small RCTs but no COVID-specific preclinical data, that would earn a NO GO?
 - You won't have many preclinical assays for immunomodulators
 - For "preclinical data," change NONE to "0" rather than NO GO
 - Toxicity should be covered with safety
- Key Criteria Scoring Post Triage: Stage 2
 - For drug/drug interactions – change "none" to "clinically nonsignificant" / "no significant drug interactions"
 - Availability/scalability
 - How to judge manufacturing capability? Objective way of assessing production capability?
 - Feasible to access expert advice as needed
 - Better to not include availability/scalability in scoring process?
 - Decision to keep this criterion
 - Can discuss further with Committee if requires further discussion
 - Safety
 - Working Group members to view "notes on criteria" description
- (b) (4) discussion of suggestions for improvement – will continue to look for options
- RFI/survey

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting, Key Takeaways

Thursday, May 14th, 2020

- “summary of existing data in humans” – clarify that this is for any indication, not just for COVID
- Explicitly add a safety category
- Add an area where people can put references to other data available/ linking out
- Specify preclinical data is for SARS COV2
- Need questions on clearance under PK/PD
- Add patient population studied for “clinical data” type of trial
- For “Clinical data,” change:
 - A – questions for trial
 - B – questions for “other”
- (b) (4) request – working group to ask clinical trial capacity group to offer this up to sites to gauge interest

Chatbox

From Peter Wung to Everyone: 01:17 PM

Are we still taking the top 2-3 scored or do we need to have a quality score cut-off?

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting 9, Key Takeaways

Tuesday, May 12th, 2020

Action Items

Action Items		
	Information	POC
1	Update scoring system based on feedback captured today	Stacey Adam/ Elizabeth Kim
2	Communicate postponing of IL-6 decision to ACTIV leadership	Stacey Adam
3	Follow up on requests for landscape analysis/potential AI or other support for quick turn research	Stacey Adam/ Elizabeth Kim
4	Share RFI draft with Working Group by this Thursday, 5/14	Sarah Read and Eric Hughes/ Stacey Adam

Key Takeaways

- Updates to Sub Group on revised agent prioritization process, incorporating feedback from prior sessions
- Stage 1 of scoring
 - Include links to other peer reviewed information in survey
 - Who will conduct the triage? Will we subdivide by agent and allow subsets of experts to triage? Preference for experts in subsets to conduct triaging.
 - About the trials – if “none,” give zero score rather than making it a “no go.”
 - Concern about doubling the scores to weight heavier
 - “Data from one or more small RCT’s” discussion
 - Have RCT as a 6, everything as a 2, and nothing as 0
 - Heavily weight if we do have valid RCTs
 - Pharmacodynamic properties – we may be getting not efficacy data from smaller trials but a better understanding of PD endpoints that suggest viral efficacy
 - Create two different scoring systems for the subsets. For example, for immunomodulators, rationale is more relevant; for antivirals, preclinical data is more relevant, and clinical data is a lower scoring scale.
 - Split up to “clinical” and “preclinical”
 - “SARS-COV2 Trials” – change to “clinical data”
 - NHLBI is taking the lead on anticoagulants
 - Adjust clinical data “no go”: if there have been clinical trials for different indications/ tried elsewhere like in China and have been found not to be effective, then no go
- Stage 2 of scoring

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group Working Group Meeting 9, Key Takeaways

Tuesday, May 12th, 2020

- Availability/scalability modifications
- Safety – “minor concerns” clarify meaning – be careful not to downgrade drugs for small concerns
 - No ability to judge – 0
 - Major concern – no go
 - Everything else – 1
 - Drop down menu suggestion
- IL-6 inhibitor request
 - Optics of choosing one company could be detrimental
 - There are at least 13 clinical trials in play; in France – trial has reached conclusion. Other ways of ensuring that there’s an adequate patient-base to make these decisions?
 - We should focus less on company. Instead, suggestion to assess if IL-6 is reasonably good candidate, and then find out about trials that are ongoing and find out about status, connect with those companies, and then determine whether there’s sufficient randomized trials ongoing, assess patient populations.
 - UK study
 - Need for landscape analysis – direct access to trials going on globally, access to contacting companies as to where the studies are
 - Do not want to make an uninformed decision

Chatbox

From Peter Wung to Everyone: 01:26 PM

For the second stage, you could make two options between clinical vs. preclinical scoring depending on the compound.

From Ruxandra Draghia-Akli to Everyone: 01:49 PM

<https://www.recoverytrial.net/>

The Recovery trial 5000 patients, Tocilizumab is one arm.

In the UK

From Libby Higgs to Everyone: 01:54 PM

Team (b) (4) has already done this for the USG. We need to ask for the information

From Stacey Adam to Everyone: 01:55 PM

Thanks, Libby! That's helpful

Do you know which USG?

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group

Sub Group Meeting, Key Takeaways

Monday, May 11th, 2020

Key Takeaways

- Group consensus on 85% power
- Moderate 2 (aka Moderate-Aggressive) in efficacy and futility bounding
- FDA is supportive of 85% power, the choice of Moderate 2, and okay without multiplicity adjustments in this situation, given the pandemic.

Opening

- Overview of presentation from (b) (4), (b) (6) and colleagues from (b) (4) which was delivered to subset of Master Protocol Sub Group on Saturday, 5/9
- Overview of (b) (4)
- (b) (4), (b) (6) and (b) (4) team carried out simulations to inform decision on interim analyses.

(b) (4) Results

- Made basic assumptions about (b) (4)

- (b) (4)
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- Then considered Group Sampling (b) (4)

- (b) (4)
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ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Sub Group Meeting, Key Takeaways

Monday, May 11th, 2020

- (b) (4)
- (b) (4) :
 - (b) (4)
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- Graphical presentations for – **SEE SLIDES FROM STATISTICAL TEAM FOR DETAIL**
 - (b) (4)
- If we were to give (b) (4) ze
 - On industry side, (b) (4)
- (b) (4)
- On Saturday, 5/9, sub team agreed on (b) (4)
 - (b) (4)
- (b) (6) (b) (4)
(b) (4)
 - (b) (4)
 -

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Sub Group Meeting, Key Takeaways

Monday, May 11th, 2020

(b) (4)

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■ (b) (4)

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- If we stay with 85%, group consensus on Moderate 2 scenario?

(b) (4)

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- Elliott Levy – offer to support with (b) (4)'s team
- FDA
 - Suggest we stick with 85% power
 - Stick with moderate 2 in efficacy bounding
 - FDA statisticians are okay without multiplicity adjustments in this situation, given the pandemic

ACTG presentation on outpatient master protocol

- Overview of objectives and activities – **SEE SLIDES FROM ACTG FOR DETAIL**
- Rapidly and efficiently evaluate multiple potential therapeutics for COVID-19 in an outpatient setting
- Phase II objectives: Determine efficacy of an agent to reduce the duration of COVID-19 symptoms OR viral shedding through 21 days after study entry.
 - Equal randomization in all arms

Monday, May 11th, 2020

- Sample size ~ 110 participants per arm
- Primary endpoint at day 20
- Endpoints based on symptoms and virologic outcomes
- Another trial A5395 looking at hydroxychloroquine and azithromycin
- Phase III objectives: Determine if an agent will prevent the composite endpoint of either hospitalization or death by 21 days after study entry.
 - For those agents that might be graduated, will have randomization
 - About 1,000 participants in each arm
 - Will all be compared to placebo arm (1000 participants) that's ongoing
 - Same assessments over time as in phase II
 - Endpoints based on hospitalization and death
 - 200 participants will be site selected to undergo intensive NP and nasal swab blood collections to investigate virology and inflammation.
- ACTG Network
 - In place, supported by NIAID
 - 35 domestic sites, capacity for outpatient trials, international sites
 - Central IRB, contracting with sites, data center and support for trial in place
 - A5395 trial can be expanded to additional sites if needed
- Questions from the Master Protocol Sub Group
 - Speak more to clinical endpoints for Phase II? FDA thoughts?
 - ACTG is putting in the questions to the FDA around what they think about the clinical endpoints. A participant comes in with COVID-19 symptoms, graded between mild, moderate, or severe at entry. Participant may develop new symptoms across study. ACTG is interested in the duration of symptoms and how change from moderate to mild to resolution over time, especially at 20th day.
 - People may have one symptom that gets worse, and one that gets better, etc. How will this work with multiplicity of endpoints?
 - Have secondary endpoints – looking at area under the curve for those symptoms
 - All symptoms have to improve – it's time to resolution or all symptoms or time to improve for all symptoms
 - Endpoints being used for Phase II is different from that of Phase III? At end of Phase III, are inferences from both Phases II and III or just Phase III?
 - Yes. Phase II endpoint is symptoms duration and NP shedding of virus.
 - For Phase III, endpoint is composite endpoint of hospitalization and death.

Monday, May 11th, 2020

- Will ask FDA if they want symptoms in the phase III portion as well as a primary endpoint
- Consensus among team members was that we need to have a clinical endpoint. The idea is to try to identify drugs that are more like what pharmaceutical companies normally develop, drugs that have 90% chance of success, not 70% chance of success.
- The goal is to try to have a 200-patient trial that identifies a drug that has antiviral and clinical impact, and then to have a phase III trial with less risk of being modestly active or inactive. They are distinct trials.
- FDA:
 - Virologic endpoint is not really valid yet and is a surrogate.
 - Joan Butters – very interested in virologic and clinical endpoints; in terms of drug supply, anything we bring forward, we'd have enough supply certainly for 1,000 patient studies.
- Reasoning behind separate phase II and phase III?
 - We can do this in a way where phase II move into phase III. Challenge in the outpatient: more challenging to get measurements. The 2,000-patient phase III trial will have much lower "touch" interaction with the sites due to logistics, PPE, willingness for individuals to come back to health care center multiple times. So, design of doing the phase II first which is more interactive and requires more from all participants is one of the reasons we divided the study in this way. We didn't think we'd gain that much in efficiency.
 - Can cycle through a lot of early stage drugs quickly and get answers before expanding patient population
- Timing of study?
 - Within next 1-2 weeks, will have protocol ready for FDA
 - Haven't selected agents yet, but think will start with monoclonal antibodies
 - Working with ACTIV to determine agents most useful for outpatients to start cycling through the protocol
 - Optimistically aiming for end of June to be up and running
 - Interested in what ACTIV committee proposes as high priority agents
- 15% a good estimate? Any sample size re-estimation built in?
 - ACTG is learning from the A5395 COVID trial of HCQ and Azithromycin, according to which 15% is a good estimate.
- Have a minimum of patients that are high risk vs. those at lower risk?
 - Want 50% of people to fall in high risk category, which is same as HAS COVID trial – so over the age of 60 or with a co-morbidity

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Sub Group Meeting, Key Takeaways

Monday, May 11th, 2020

- Another reason why Phase II separate from phase III. Phase II focus is to identify those who are shedding virus quickly. While we'll stratify for higher risk, won't require it; and will try to enroll people that are closest to symptom start. Phase II is more of a proof of principle-type approach. Phase III enriched for the higher risk people.

Accelerating COVID-19 Therapeutic Interventions and Vaccines

ACTIV Partnership Leadership Group Meeting

May 6, 2020, 3:30 – 5:00 pm ET

May 7, 2020



This meeting summary was prepared by Lucas Smalldon, MA, Rose Li and Associates, Inc., under contract to the Foundation for the National Institutes of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH.

Meeting Summary

The Leadership Group overseeing the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review progress made since program launch on April 3, 2020. Dr. Francis Collins, Director of the National Institutes of Health, opened the meeting by announcing the creation of a new ACTIV Executive Committee (EC) to meet bi-weekly beginning 2 weeks from today, and to be co-chaired by Dr. Collins and by Dr. (b) (4), (b) (6) from (b) (4). EC members will include Drs. Anthony Fauci from the National Institute of Allergy and Infectious Diseases (NIAID), Gary Gibbons of the National Heart, Lung, and Blood Institute (NHLBI), Janet Woodcock of the Food and Drug Administration (FDA), (b) (4), (b) (6) of (b) (4), and (b) (4), (b) (6) of (b) (4). Once bi-weekly EC meetings begin, this larger Leadership Group could potentially shift to a monthly meeting schedule, although that is yet to be decided.

Following Dr. Collins' announcement of the EC, the Leadership Group received updates from Co-Chairs of all four ACTIV Working Groups (WGs), which cover the following focus areas: (1) Therapeutics-Preclinical; (2) Therapeutics-Clinical; (3) Clinical Trial Capacity; and (4) Vaccines. The Leadership Group discussed progress made by each WG so far and consulted the WG Co-Chairs about their ongoing activities and further action plans.

Therapeutics-Preclinical WG

Christine Colvis, PhD, National Center for Advancing Translational Sciences (NCATS); John Young, PhD, Roche

The Therapeutics-Preclinical (TX-Preclinical) WG has identified five strategic objectives to accelerate testing of compounds for entry into clinical trials: (1) Generate a master inventory of necessary testing resources to support generation of preclinical data; (2) Create a national strategy for use of limited preclinical resources during the COVID-19 crisis period (to include a master protocol); (3) Establish a virtual preclinical *in vitro* and *in vivo* testing network for therapeutic sponsors to access preferred or limited resources (the WG considers objectives 2 and 3 to be components of an overarching pandemic response framework); (4) Establish standard protocols to support preclinical compound prioritization (including an expert review panel); and (5) Create a public database for sharing *in vitro* and *in vivo* model characteristics and data.

Thus far, the WG has compiled an inventory of appropriate available nonhuman primate (NHP) resources and defined a preliminary prioritization strategy for their use and has also defined a prioritization framework for antivirals using available *in vitro* data. Next, the WG will assemble its expert panel for preclinical compound prioritization (having already solicited interest among many top global experts) and will also identify potential platform providers and gather criteria for its preclinical database.

NHP National Strategy Overview

The WG's preliminary national strategy for NHP research on SARS-CoV-2 aims to maximize the research value of scarce NHP testing resources. The strategy establishes a staged approach to

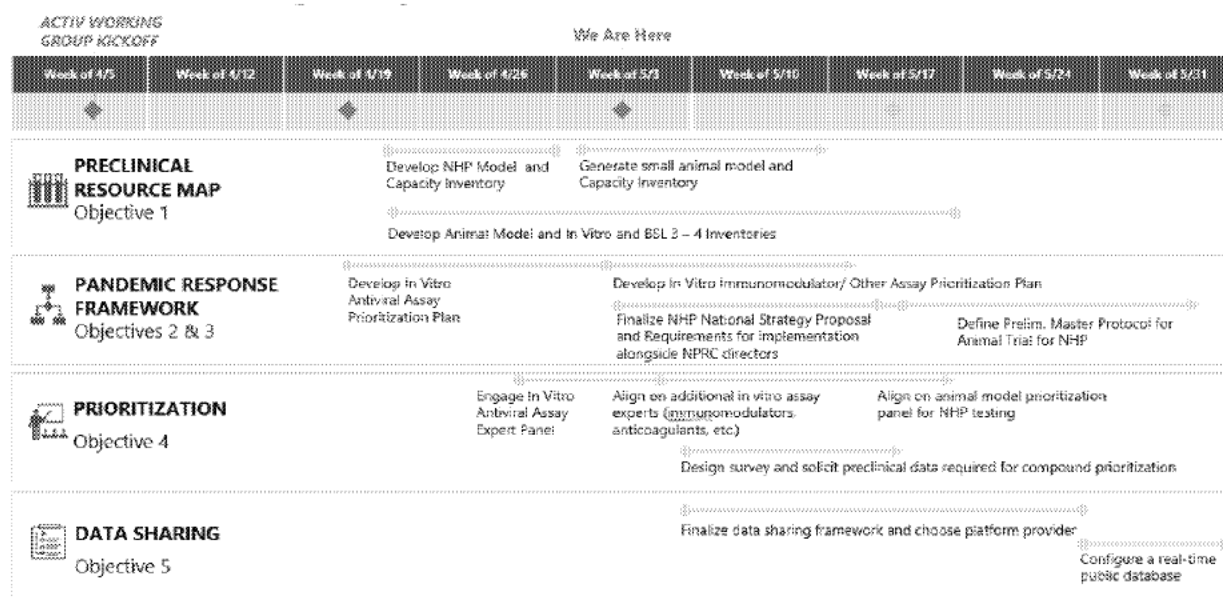
align animal resources with immediate need, defines points of interaction between the ACTIV expert panel and the National Primate Research Center (NPRC) Directors, and proposes clear guidance for animal use and therapeutic testing. The NHP national strategy was driven by ACTIV's drug class prioritization (e.g., NHPs to be used to test vaccines and severe symptom modulators, but not antivirals), disease model stage of validation, resource availability (e.g., African Green Monkeys versus Rhesus macaques), and the severity of COVID-19 disease across animal species. Thus far, African Green Monkey models hold the most promise because animals infected with SARS-CoV-2 appear to exhibit acute respiratory distress syndrome (ARDS); however, these animals are in particularly short supply (perhaps numbering a few hundred, versus the thousands of available Rhesus macaques). Implementing the NHP strategy will require additional financial resources—for example to build NPRC infrastructure and conduct model validation studies—and will also require close collaboration with NPRC Directors.

Accelerating Preclinical Antiviral Screening

The WG has established a standard operating procedure (SOP) to accelerate preclinical (*in vitro*) antiviral screening and prioritization during the COVID-19 response. The WG has delineated critical versus non-critical components (i.e., “must-haves” versus “nice-to-haves”) of preclinical antiviral screening, recommended primary and secondary assay thresholds for such screening, and identified clinical data required for an accelerated screening path. The WG is also working to develop similar SOPs for testing immunomodulators and other disease-modifying agents.

TX-Preclinical WG Timeline

The timeline below summarizes the WG's progress thus far and imminent planned activities, such as finalizing its data sharing framework and choosing a platform provider for its publicly available database.



Discussion

Following their presentation, the WG Co-Chairs answered Leadership Group questions. Dr. Collins also highlighted that, although the TX-Preclinical WG has focused its NHP discussions around therapeutics testing, NHP resources will also be crucial for testing vaccines.

Small Animal Models

Although the TX-Preclinical WG has focused mainly on NHP models, it has established a Small Animal Models Subgroup that has explored potential uses for models such as the Syrian hamster and the hACE2 transgenic mouse. However, the validity and usefulness of such models for studying COVID-19 pathology in humans remain largely unknown. Mouse models have been useful for studying SARS-CoV-2 replication but not COVID-19 disease phenotypes (i.e., mice do not display much disease pathology), whereas Syrian hamsters exhibit more severe disease.

Evaluating NHP Testing Applications

The process for asset-holders (i.e., companies and academic labs) to submit and evaluate proposals to test agents in NHPs will largely depend on which agents are prioritized by the other ACTIV WGs (e.g., TX-Clinical) and on judgments made by the preclinical evaluation expert panel to be established by the TX-Preclinical WG.

De-Prioritization of Antivirals for NHP Testing

The TX-Preclinical WG decided to prioritize immunomodulators over antivirals for testing in NHPs. This decision assumed that antiviral efficacy against SARS-CoV-2 could be revealed by *in vitro* or small animal model testing and thus would not require NHPs, whereas testing of immunomodulators would require animals with immune systems that more closely resemble that of humans.

Data Sharing Platform

One aim of the envisioned preclinical data sharing platform is to enable insights across multiple experiments on multiple agents. Limited preclinical testing resources constrain the complexity of experiments conducted in parallel but establishing a shared platform to integrate data from existing and ongoing studies may help investigators to identify important clues about COVID-19 pathogenesis and potential treatment approaches not apparent from any single study. The data sharing platform will be designed not only to circulate data, but to provide information on how data were generated, thereby aiding interpretation and comparison.

Therapeutics-Clinical WG

(b) (4), (b) (6); MD, PhD, (b) (4) Sarah Read, MD, NIAID

Agent Prioritization

The TX-Clinical WG has completed Wave 1 of agent prioritization, which focused on selecting FDA-approved compounds for potential repurposing, to be tested under an amendment to the NIAID-sponsored Adaptive COVID-19 Treatment Trial 2 (ACCT-2) protocol, to be called ACTT-3. The TX-Clinical WG's Agent Prioritization Committee (APC) prioritized compounds in three primary classes: (1) antivirals; (2) immunomodulators/host-targeted therapies; and (3)

symptomatic/supportive therapies (e.g., anticoagulants). After initial triage of candidate agents by mechanism of action (MOA) and clinical readiness, the APC identified 39 agents to be scored using in-depth prioritization criteria, which included evaluation of MOA rationale and of any ongoing SARS-CoV-2 trials; availability of preclinical data; assessment of PK/PD, safety data, and drug-drug interactions; and confirmation of sufficient availability/scalability of the drug.

(b) (4)



The APC selected three immunomodulators and three anticoagulants, eliminating all antivirals for this first wave. Although agent prioritization Wave 1 focused on pre-approved agents with repurposing potential to treat inpatients only (i.e., to be tested immediately in phase III confirmatory trials in hospitals), subsequent agent prioritization waves will consider a wider range of therapies at various stages of development and targeting various patient populations, including outpatients and unaffected individuals (i.e., prophylaxis). Agent ruled out for this wave can be reconsidered in future assessments by the group.

In addition to the six prioritized agents discussed above, the TX-Clinical WG has identified two more therapeutic candidates already being tested under other master protocols that it suggests incorporating under the ACTIV umbrella for easy comparison with the other agents being tested by ACTIV: these therapies are Baricitinib, which is being tested under ACTT-2, and Hyperimmune Intravenous Immunoglobulin (hIVIG), which is being tested under INSIGHT Protocol 12.

Master Protocols

Drug Repurposing Master Protocol

The Master Protocol (MP) Subgroup had originally planned to test all agents prioritized during Wave 1 under ACTT-3. However, details of the ACTT-3 design could not be finalized until the final set of prioritized agents was known. The MP Subgroup has now developed a revised plan to test the three immunomodulators and three anticoagulants (and no antivirals) selected. To simplify trial design, the selected immunomodulators will be tested under ACTT-3, whereas the

selected anticoagulants will be tested under a separate master protocol that is being developed and led by NHLBI and the National Institute of Neurological Diseases and Stroke (NINDS). In addition to simplifying trial design, testing the selected immunomodulators and anticoagulants in separate protocols will support standardized primary endpoints (i.e., time to recovery) with customized secondary endpoints appropriate to each trial. Moreover, the two protocols can be conducted in different trial networks well-suited to the specific agents.

The ACTT-3 design is now being finalized to account for the list of selected immunomodulators and for the recent Remdesivir trial results. It will be an adaptive randomized placebo-controlled confirmatory trial of immunomodulators targeting hospitalized adults diagnosed with moderate to severe COVID-19. The trial will include up to 100 clinical sites and will compare each agent to Remdesivir plus a placebo as the standard of care (SoC). Patients will be randomized into the four treatment groups in a 1:1:1:1 ratio. For enough statistical power, ACTT-3 will need to enroll a total of 2,066 patients across all four study arms.

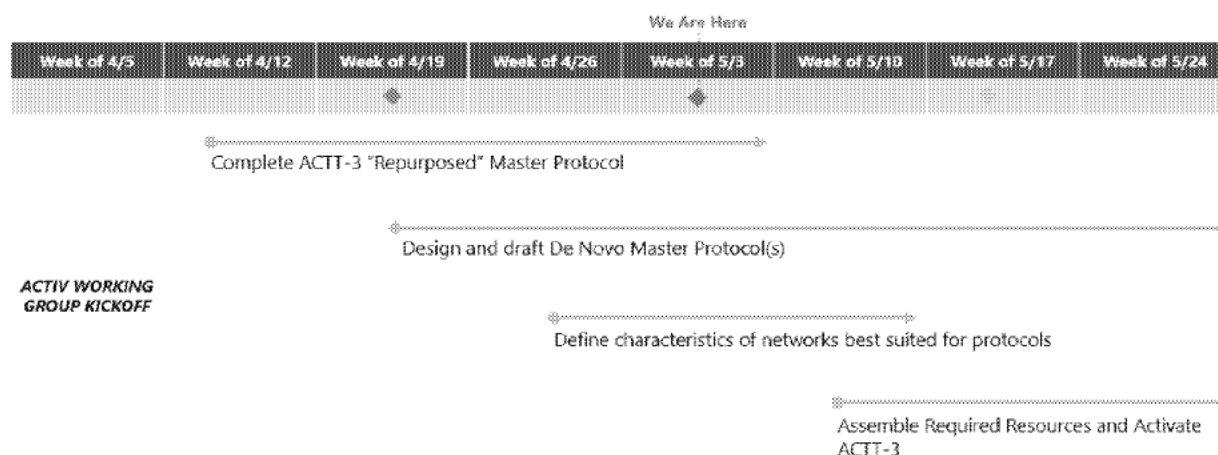
The MP Subgroup will also conduct interim analyses, such as blinded sample size re-estimation at 10 percent enrollment, and evaluation of efficacy and futility at 33 percent and 67 percent of enrollment for potential early cessation of the trial.

ACTIV De Novo Master Protocol

The MP Subgroup previously decided that while designing its drug repurposing master protocol, it would concurrently begin development of a *De Novo* 'Gold Standard' master protocol for testing agents selected during future APC prioritization waves. The design of this more comprehensive master protocol is expected to be completed by July 2020. It will enable ACTIV to test a broader range of therapeutics (including earlier phase antivirals and immunomodulators and SARS-CoV-2-specific monoclonal antibodies) targeting more diverse patient populations than was possible under the rapid drug repurposing protocol. This *De Novo* protocol will facilitate seamless Phase II-to-Phase III progression and will function under a single Institutional Review Board (IRB).

TX-Clinical WG Timeline

The timeline below captures the WG's progress thus far and additional planned activities in its development of the ACTT-3 and *De Novo* master protocols:



As it works to match its master protocols to existing clinical trial networks, the TX-Clinical WG is also liaising with the Clinical Trial Capacity WG.

Discussion

Following their presentation, the WG Co-Chairs responded to Leadership Group questions and discussion points.

Selection of (b) (4) for Testing

Dr. (b) (4), (b) (6) expressed surprise at the APC's selection of (b) (4) — (b) (4) — given how often this drug class has failed in clinical studies for other indications, suggesting that this agent class holds no biological relevance for humans. Drs. (b) (4), (b) (6) and (b) (4), (b) (6) explained that (b) (4) are elevated in ARDS patients, and that patients with SARS-CoV induced ARDS and cytokine storm have been observed to have (b) (4)

(b) (4) was a risk factor for poor outcomes and death in Hong Kong and Beijing Chinese SARS patients.

Unlike some other agents considered, (b) (4) is not being studied yet by other research groups despite its availability and promising safety profile. Should there be data that suggest it is not working, our Master Protocol Subgroup is designing a trial that will allow for the relative quick closure of trial arms with agents that show no effect.

Standardization of Time to Recovery

To support standardization of time to recovery as a primary endpoint across master protocols, the TX-Clinical WG is currently evaluating the ordinal scale or a defined dichotomous scale as an endpoint measure.

Limited Availability of Remdesivir

Although the TX-Clinical WG cannot guarantee adequate supplies of Remdesivir to execute its proposed ACTT-3 master protocol, Dr. Woodcock confirmed that FDA can assist in obtaining an adequate supply for ACTIV trials.

Clinical Trial Capacity WG

Elizabeth Desrosiers, MS, PMP, Merck; Michael Kurilla, MD, PhD, NCATS

The Clinical Trial Capacity (CTC) WG aims to develop an inventory of clinical trial capacity (including networks run by NIH Institutes and Centers, industry, and other organizations) that will serve as a guide for the settings in which to implement effective COVID-19 clinical trials. Thus far, the WG has developed inventories of networks and contract research organizations (CROs), produced survey questions to identify capabilities for networks as well as for individual sites within them (a CRO survey is pending), and assessed the ACTT-1 and 2 trial operations to identify novel/scalable operations enhancements and efficiencies to support a repurposed ACTT-3 protocol (e.g., the WG has begun contacting vendors that might provide eConsent services to trial sites).

The CTC WG surveyed clinical networks thought to be 'shovel-ready' (i.e., those that could become fully functional in 6 weeks or less) and plans to deploy its CRO survey on May 8. The WG also plans to develop an inventory of academic, industry, and additional NIH networks, and to deploy another survey to those networks and their sites. The CTC WG will eventually maintain a global database of networks and sites that can be overlaid onto Johns Hopkins University's geographical COVID-19 case data to see how outbreak hotspots map onto clinical trial capacity to facilitate matching of studies to clinical networks and sites.

(b) (4)

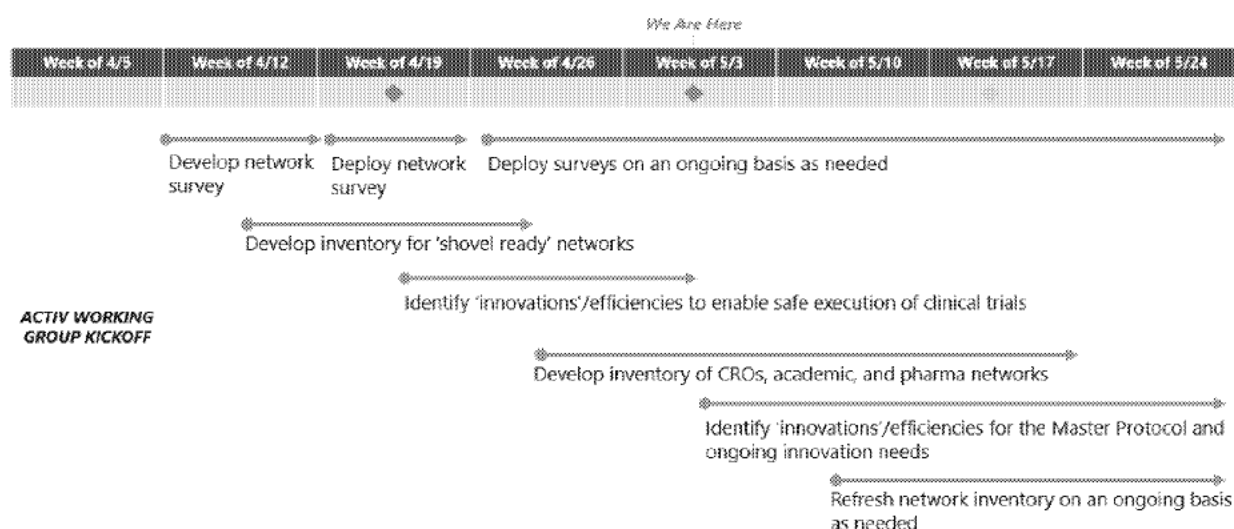


The CTC WG is exploring creating a unified contract mechanism to facilitate smooth and rapid onboarding of new networks to conduct ACTIV clinical trials. Networks that have experience with the use of a central IRB may be more easily onboarded, so the WG is also considering this experience in its rankings. Dr. Kurilla highlighted that over 80 percent of surveyed sites are either already conducting COVID-19 trials or have such trials planned, which could potentially disturb ACTIV's ability to secure its desired capacity from its top-ranked networks and sites.

Subsequent surveys will collect information from additional networks that may require additional support (even if minimal) to initiate trials, in addition to networks that typically enroll special patient subpopulations (e.g., pregnant women, rural residents).

Clinical Trial Capacity WG Timeline

The timeline below summarizes the CTC WG's progress thus far and other planned activities.



Discussion

Following their presentation, the WG Co-Chairs responded to Leadership Group questions and discussion points.

U.S. Department of Veterans Affairs Master Protocol Efforts

Dr. Rachel Ramoni of the United States Department of Veterans Affairs (VA) informed the CTC WG Co-Chairs about ongoing VA efforts to develop master protocols for COVID-19 clinical trials. VA is eager to collaborate with ACTIV and would be interested in potentially aligning endpoints with ACTIV's master protocols to support data integration and comparability. The MP Subgroup of the TX-Clinical WG is also actively discussing its master protocol designs with representatives from VA to align efforts.

Vaccines WG

Kathrin Jansen, PhD, Pfizer; Douglas Lowy, MD, National Cancer Institute (NCI)

The Vaccines WG aims to speed evaluation of candidate vaccines and enable rapid approval by pursuing the following three priorities: (1) Develop a harmonized master protocol efficacy trial to accelerate traditional vaccine approval timelines; (2) Identify biomarkers and other evidence needed to accelerate approval and authorization of vaccines; and (3) Efficiently evaluate cross-cutting vaccine safety questions.

Harmonized Master Protocol for Vaccine Evaluation

The Vaccines WG's newest remit is to create a harmonized master protocol for vaccine testing. This master protocol will follow a phase II-III adaptive platform trial design for the simultaneous assessment of multiple candidate vaccines at different stages of development, with the ability to ingest new vaccine candidates when they become ready and to advance promising candidates to phase III while eliminating failed candidates. The WG has established a subgroup that includes representatives of FDA, vaccine manufacturers, and NIH Institutes and Centers, as well as various extramural NIH investigators, to focus on these efforts. NIAID is expected to provide a draft master protocol around mid-May.

Key challenges in developing this harmonized master protocol for vaccines include selection of appropriate endpoints and populations, design of arms for testing multiple vaccine candidates taken into the trial at different times and stages of development, identification of appropriate sample size and number of participants per arm (and of clinical networks and sites to support the studies), and determination of what constitutes a protective immune response and selection of appropriate clinical assays to measure it.

Accelerated Authorization and Approval of Vaccine Candidates

Given its goal of accelerating authorization/approval of SARS-CoV-2 vaccines, the Vaccines WG is considering ways to create interim data packages on promising vaccine candidates before its planned phase III clinical efficacy studies are complete. The WG is working to map pathways and requirements for possible authorization or approval during phase II development. For example, following FDA regulations, accelerated approval “may be based on adequate, well-controlled clinical trials establishing an *effect on a surrogate endpoint* that is reasonably likely [...to predict clinical benefit],” whereas an Emergency Use Authorization may be issued in cases of “serious or life-threatening disease”, or when a vaccine “may be effective”, or when its “known and potential benefits outweigh the known and potential risks” associated with it, or when “no adequate, approved, and available alternative” exists. Potential types of evidence to support these interim data packages include clinical immunogenicity, phase II efficacy, and animal model immune protection data, among others. More detailed plans on acceleration efforts will be forthcoming.

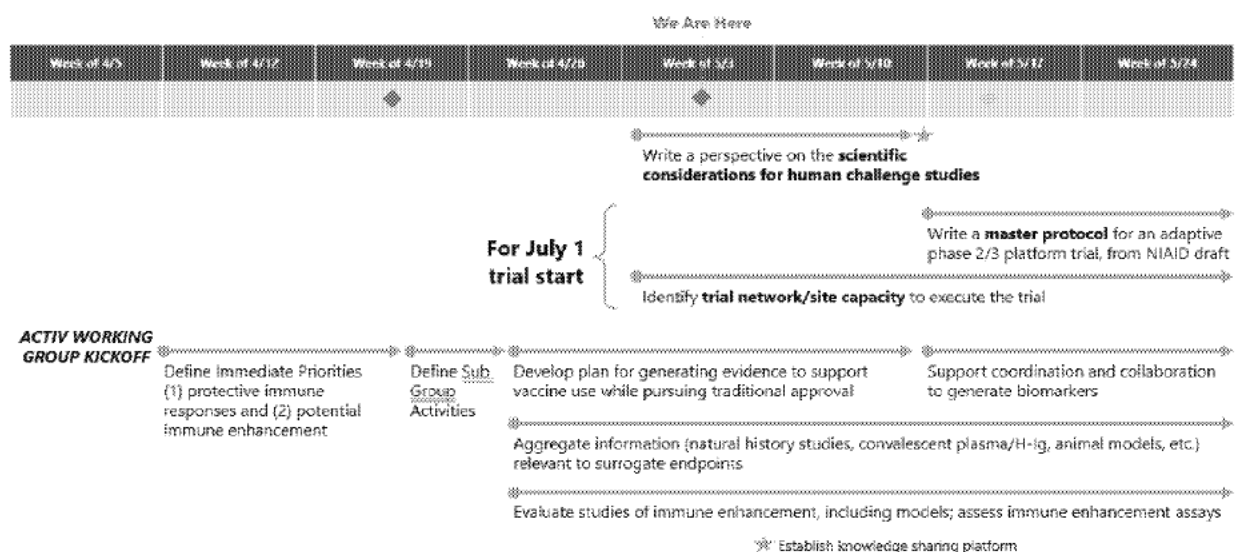
White Papers on Vaccine-Associated Immune Enhancement

Because some misperceptions of data surrounding vaccine-associated immune enhancement are common among certain key constituencies, the WG will also address questions related to

these theoretical concerns, and their implications for COVID-19 vaccines, via white papers for target audiences. The WG will provide informed reviews of data *but will not offer guidance*. Target audiences will include less experienced vaccine developers and regulatory authorities; COVID-19 vaccine development funders; normative bodies, industry groups, and other opinion leaders; and science journalists and the public.

Vaccines WG Timeline

The timeline below summarizes the WG's progress thus far and upcoming planned activities, such as writing a perspective on the scientific considerations for human challenge studies and assessing NIAID's draft master protocol for an adaptive phase II-III platform trial for vaccines.



Discussion

Following their presentation, the WG Co-Chairs responded to Leadership Group questions and discussion points.

Strategy for Comparing Candidate Vaccines

Dr. Dolsten highlighted the difficulties of comparing multiple candidate vaccines that begin at different timepoints. Although the design has not been finalized, Dr. Lowy encouraged thinking of the vaccine harmonized master protocol at least at this point in time as consisting of several "semi-independent, partially overlapping sequential trials" that Dr. Corey emphasized are "totally harmonized." The WG's efforts are being supported by statistical experts who are helping to ensure the harmonized master protocol is designed to produce comparable outcomes across vaccine candidates. Another important consideration is blinding, especially because different vaccine candidates require different delivery mechanisms (e.g., syringe versus device).

Overall Leadership Group Feedback

ACTIV Leadership Group members congratulated the WGs on their progress, highlighting how quickly ACTIV has advanced since its initial launch on April 3, 2020. Dr. Dolsten also noted that the WGs have had to make many decisions while pursuing their respective remits, and that ACTIV would benefit from documenting the rationales behind as many of those decisions as possible to help representatives of the partnership to justify the choices made.

Dr. Collins noted that much of the discussion in the meeting is still pre-decisional and needs to be communicated with appropriate discretion. He encouraged them to direct further questions, comments, or concerns either to (b) (6) or to (b) (6)

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader)*

Christopher P. Austin, MD, *Director, NCATS, NIH*

Carlos Castillejos, *Vice President External Affairs Science & Medicine, J&J*

Marco Cavaleri, *Head of Office, Anti-infectives and Vaccines, EMA*

Tomas Cihlar, PhD, *VP of Virology, Gilead Sciences*

Amanda Cohn, MD (Capt., USPHS), *Acting Director, National Center on Birth Defects and Developmental Disabilities (NCBDDD), CDC*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*

Gary Disbrow, PhD, *Director, Division of CBRN Countermeasures, HHS and Acting Director, BARDA*

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Maria Freire, PhD, *President and Executive Director, FNIH*

Thomas J. Hudson, MD, *Vice President of Oncology Discovery and Early Development, AbbVie*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Robert Johnson, PhD, *Director, Division of Influenza and Infectious Diseases, BARDA/ASPR/HHS*

Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

Peter Marks, PhD, *Director, Center for Biologics Evaluation and Research, FDA*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID*

John Mascola, MD, *Director, Vaccine Research Center, NIAID, NIH*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Steven Paul, MD, *Chief Executive Officer and Chairman of the Board, Karuna Pharmaceuticals*

Roger M. Perlmutter, MD, PhD, *EVP and President, Merck Research Laboratories*

Robert M. Plenge, MD, PhD, *SVP, Research & Early Development and Head, Immunology, Cardiovascular, Fibrosis, and Global Health Thematic Research Center, Bristol-Myers Squibb*

Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*

Rachel B. Ramoni, DMD, ScD, *Chief Research and Development Officer, Department of Veterans Affairs*

Guido Rasi, *Executive Director, European Medicines Agency (EMA)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

John C. Reed, MD, PhD, *Executive Vice President, Global Head of Research & Development, Sanofi*

Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*

Daniel M. Skovronsky, MD, PhD, *Senior Vice President and Chief Scientific Officer, Eli Lilly and Co.*

Peter Stein, MD, *Director, Office of New Drugs, FDA*

Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson*

Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*

Michael J. Talley, Brig. Gen., *Commanding General, U.S. Army Medical Research and Development Command and Fort Detrick, MD*

John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*

Debara Lyn Tucci, MD, *Adjunct Professor, Department of Surgery, Duke University School of Medicine*

Rupert Vessey, DPhil, *President of Research and Early Development, Bristol-Meyers Squibb*

Herbert (Skip) Virgin, MD, PhD, *EVP Research and CSO, Vir Biotechnology*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

Patrice Allen-Gifford, *Director, Executive Secretariat, NIH*

James M. Anderson, MD, PhD, *Director, Division of Program Coordination, Planning, and Strategic Initiatives, NIH*

Diana Bianchi, MD, *Director, National Institute of Child Health and Human Development (NICHD), NIH*

Patricia Flatley Brennan, RN, PhD, *Director, National Library of Medicine, NIH*

John T. Burklow, *Associate Director for Communications and Public Liaison, NIH*

Noni Byrnes, PhD, *Director, Center for Scientific Review, NIH*

Robert H. Carter, MD, *Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH*

Richard W. Childs, MD, *Clinical Director, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Joshua Denny, MD, MS, *Chief Executive Officer, All of Us Research Program, NIH*

Gary H. Gibbons, MD, *Director, NHLBI, NIH*

Roger I. Glass, MD, PhD, *Director, Fogarty International Center and Associate Director, International Research, NIH*

Adrienne Hallett, *Associate Director for Legislative Policy and Analysis, NIH*

Richard J. Hodes, MD, *Director, National Institute on Aging (NIA), NIH*

George F. Koob, PhD, *Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA), NIH and Professor, Scripps Research Institute*

Helene Langevin, MD, *Director, National Center for Complementary and Integrative Health (NCCIH), NIH*

David Lankford, JD, *Deputy Associate General Counsel and Chief, NIH Branch of HHS Office of General Counsel, NIH*

Michael Lauer, MD, *Deputy Director for Extramural Research, NIH*

Griffin P. Rodgers, MD, *Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH*

Tara A. Schwetz, PhD, *Associate Deputy Director, NIH*

Santa Tumminia, PhD, *Acting Director, National Eye Institute (NEI), NIH*

Hannah Valentine, MD, MRCP, *Senior Investigator, NHLBI, NIH*

Nora Volkow, MD, *Director, National Institute on Drug Abuse (NIDA), NIH*

Carrie D. Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Richard Woychick, PhD, *Acting Director, National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program, NIH*

Stacey Adam, PhD, *Science Program Manager, FNIH*

Greta Gorman, *Director of Communications, FNIH*

Abbey Meltzer, MPS, *Vice President of Communications and Events, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

Stephanie James, PhD, *Senior Vice President of Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, *Consultant, Deloitte*

Margaret Anderson, *Managing Director, Deloitte*

Olivia Elsaid, *Consultant, Deloitte*

Nina Gonzalez, *Senior Manager, Deloitte*

Elizabeth Kim, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Jonathan Wachtel, *Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

There were two attendees that could not be identified: Ylesr; Emr13311

Appendix B: Additional Discussions from Zoom Chat Transcript

(b) (6) : 30:43

When will the committee be ready to consider proposals for NHP evaluation and what will the application process entail?

The team is focusing initially on model validation, which is expected to continue into August and early September with therapies that can be compared to data coming from clinical studies. If an NHP model is validated at that time, prioritize therapies could be tested as soon as September.

(b) (6) : 31:39

Do we need more NHPs for the next pandemic? Do we need to better prepare in the future? Should we be better resourcing the National Primate Centers?

If no suitable small animal model is available, NHP will be limiting.

(b) (6) : 31:40

Can the team suggest what types of experiments would provide broader learnings just than single drug or vaccine? such as creating learnings cross many products.

Discussed in the minutes.

(b) (6) : 32:19

What is the general number of NHPs we're talking about?

Discussed in the minutes.

(b) (6) : 35:30

Are you in contact with Portion Down/dstl to understand if they are also developing natural history models?

NIAID has been in communication with them and we will follow up with our NIAID working group members.

(b) (6) : 35:40

Can you say more about de-prioritization of antivirals vs. immunomodulators for NHPs - disease in the monkeys is so mild, we have thought less promising for immunomodulators?

Small animals will likely be sufficient for antivirals. (b) (5) have shown some signs of late stage severe disease and will be explored for their potential to serve as a model for immunomodulators or severe symptoms.

(b) (6) : 43:55

Did you discuss neutralizing antibodies or is it too early?

Given that SARS-CoV2 neutralizing antibodies were earlier in the development pipeline and not ready for a large Phase 3 validation study as their first test, the Agent Prioritization Committee decided that those agents should wait for the second round of prioritization in which the agents selected would be placed in an adaptive Phase II/III progressive trial design, which would allow for rapid testing and elimination of any of those compounds that do not seem to be showing a significant effect on preventing progression of the virus or aiding patients to a more rapid recovery.

(b) (6) : 48:55

What is the thinking around standardization of time to recovery?

This endpoint is the one that has been selected for both ACTT-1 and ACTT-2, as well as many other newer trials that have been designed to test COVID-19 therapeutics. It was selected for the ease of measurement for the treating physicians. The use of this endpoint for the primary endpoint does not exclude the collection and use of the 8 point ordinal scale that is being employed by other COVID-19 master protocols. We will be collecting this data as a secondary endpoint and will be able to harmonize our data to the other existing trials as all report out.

(b) (6) : 50:22

To what extent actual data with SARS-COV2 were considered for prioritization?

To the extent that data existed for a compound and could be found relatively quickly and easily in one of the public repositories of COVID-19 data, this data was reviewed and assessed by the team to help facilitate their decisions. However, for many of the compounds, especially those in the Host Targeted/Immune Modulator category there was very limited data to be found that directly related the compound to SARS-CoV2 treatment. In addition, the group found for the Antiviral category that while there were many in vitro screens for the compounds to test EC50 and other metrics, sometimes the data was conflicting and is known to be cell line specific, which made it challenging to make a definitive selection. The group was cautious and decided not to promote compounds that did not show a consistent effect.

(b) (6) : 55:04

You mentioned interim analyses. (b) (5)

We have had multiple members of the FDA CDER team engaged on our master protocol design calls, including several statisticians. They have been weighing in and counseling the team as they have been making the selection of methodology and timepoints for the interim analyses, and while we don't have final agreement, we do believe that we will be able to achieve a solution both functional for our needs and acceptable to the FDA.

(b) (6) 01:07:44

What are the criteria to select sites? is requirement to have experience in clinical trials designed to support licensure?

The ACTIV Therapeutics-Clinical Working Group will be having a conversation with the leads of the VA master protocol on May 8th. We will share information in both directions on trial design and timelines. We hope to be able to synergize efforts between our groups.

(b) (6) : 01:11:56

Given that most sites have ongoing trials, was there an assessment of potential recruitment potential/timing within the patients not already on a protocol?

(b) (6) : 01:13:07

This is (b) (6) from VA. We have a master protocol in planning and several discussions with pharma companies. Knowing when Activ will start will be critical for us. Also, knowing how many sites will be needed for Activ will also be important.

(b) (6) : 01:18:16

nice slides - Two questions:

(b) (6) : 01:24:23

Good slides and work - 1) what are the risks is comparing cross different trials starting at various time points as outcomes seems to differ in various regions due to various factors. 2) as the vaccine formats are different in procedures of RNA, DNA, protein and virus delivery systems. how do you account for this w placebo and staying blinded eg administration differ w RNA, DNA (DNA often use device). Certain delivery systems benefit from assessing whether you can re-dose or not due to anti vehicle Abs. Is that accounted for?

The goal of the study design is to compare vaccine candidates to placebo, and the trial design is anticipated to enable contemporaneous placebo comparison for every candidate. The issue you raise is a limitation for any attempted comparisons across vaccines evaluated at different times, given that as the epidemiology evolves the geographic loci of events may shift over time.

(b) (6) 01:29:16

(b) (6) the subgroup on vaccine efficacy trials recognizes this issue and the approach is to have separate harmonized trial and not one "super trial" that is both unruly to enroll and subject to more difficult issues if one vaccine has an early endpoint or early issues.

(b) (6) 01:30:14

thanks...not an easy task to pick the best of all...in separate races..good you are thinking hard on this

(b) (6) : 01:31:29

How many vaccines do you plan to test under this protocol? Do we risk going slowly with multiple vaccines recruiting in parallel within a single study, as opposed to pushing forward rapidly with only a few vaccine candidates to complete recruitment expeditiously.

We anticipate that tightly harmonized trials will enable both speed and inter-comparability of results (while noting caveats like the one (b) (6) pointed out above). Trial capacity and the best way to allocate that resource across candidates (and a mechanism for doing so) are important questions to address as we advance the implementation of this set of trials and seek to coordinate with other vaccine efficacy trial plans.

(b) (6) : 01:32:19

Will these all involve challenging healthy volunteers?

The trials will be conventional efficacy trials looking at protection against naturally incident infection. Challenge studies are not being considered. The populations in the clinical trials are part of the trial design process. As suggested by Emily Erbelding in the chat, it is a possibility that populations will be enrolled sequentially.

(b) (6) : 01:33:05

Vaccinate healthy volunteers and those at risk for worse disease (elderly) once safety can be established in latter group

(b) (6) : 01:34:19

Good progress in my view.

(b) (6) : 01:37:34

Thank you to all for this tremendous effort!

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

Action Items

Action Items		
	Information	Owner(s)
1.	<i>Around the biospecimen prioritization efforts → please have a team member take a look at the (2) slides comparing the language on the ICFs and looking at the sample collections and what might be there as a remaining sample – please give Stacey Adam feedback</i>	ACTIV Teams
2.	Please get any ICFs to Stacey as soon as possible	ACTIV Teams

Meeting Summary

- ACTIV-4a enrollment is stopped; futility boundary achieved for critically-ill patients; superiority boundary achieved for moderately-ill patients.
- Slight delay of ACTIV-4c → launch date looking to be mid-February
- THANK YOU to Will Bailey on obtaining MVI solution for blinding placebo solution from Baxter for PassItOnII and C3PO!! 😊
- Call center/ COMBATCovid traffic appear to be on the rise.
- Moving forward, the cadence of this meeting will be changed to biweekly; however, a representative from each ACTIV team needs to join.

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Updates
- Call Center Update
- Operational Challenges with Multiple Routes of Administration
- Cross-trial Operations Meeting Going Forward
- Meeting Recap

ACTIV Trial Status Updates

(Stacey Adam)

***At the request of Lynn, the sample size per arm for each of the trials is now included so that it is evident what the target enrollment is and where we are with enrollment.*

- ACTIV-1: 34 sites open; (b) (4) as of 02/03
 - Sample size (patients per arm): (b) (4)
 - Regulatory approvals received in Argentina, Peru, and Brazil
 - Version 2.0 implementation near complete; addressed all FDA comments
 - Team continues to address barriers around the CVC sub study
 - Jane Atkinson: 34 sites → required to sign the 1572; there are 5 independent hospitals
 - 10 hospitals enrolled yesterday, 02/03
- ACTIV-2: 57 sites open; (b) (4)

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

- Sample size (patients per arm): 421 for IV agents; TBD for others
- DSMB review in Feb to review data from 110 patients on Brie
- Version 4.0 to be submitted to FDA next week; there are some questions back from the FDA that need to be addressed
- Meeting with FDA on 02/11 on symptom-based endpoints
- Bill Erhardt: The Feb DSMB meeting will be a review for safety
 - The 110 patient analysis is on day 14 data; 14 days from now are needed to collect data and then PPD will need to clean the data and produce the table; this DSMB will likely occur in mid-March
 - V3 has opened; there are two sites that have opened under V3: Pittsburgh and UCLA → anxiously waiting first enrollment for V3, which includes Astra Zeneca, Sagent, and Synairgen
- ACTIV-3: 39 sites open; (b) (4) for Brie and GSK-Vir as of 02/03 (376 as of 02/04)
 - Sample size (patients per arm): 500 for ACTIV-3; 310 for ACTIV-3b
 - Sites in Poland, Switzerland, and Singapore open for Version 2.0
 - US sites start to open for Version 3.0; FPI expected this week
 - There are 2 sites open
 - ACTIV-3b submitted to FDA on 01/19 with the division of acute pulmonary care; FPI expected end of Feb/ early March
 - Laura: there appear to be 9 sites (right behind the two that are open) that are activated but not open; FP is not in yet
 - Libby: when ACTIV-2 and -3 met with the FDA earlier this week, the FDA indicated that they have higher priority items so they will not be able to have a fast turnaround time
 - By the end of March (March 29), we should have an answer on whether we have a positive clinical impact with hyperimmunoglobulin in hospitalized patients
- ACTIV-4:
 - (4a) Hospitalized: enrollment stopped – futility boundary achieved for critically-ill patients; superiority boundary achieved for moderately-ill patients → a therapeutic dose of unfractionated heparin was beneficial to patients and far exceeded the benefit of either a low-dose unfractionated or low molecular weight heparin; critically ill patients (those that went on mechanical ventilation) should not be receiving those agents because it was counter indicated
 - Libby: ACTIV-4 got mentioned on the G7
 - (4b) Pre-hospitalized: 11 sites open; (b) (4) as of 02/03
 - Hoping contract with CVS will bolster patient numbers
 - (4c) Post-hospitalized received first drug shipment on 01/05
 - Supposed to be launching imminently
 - Sample size (patients per arm): 4a – 1000; 4b – 1750; 4c – 2660
- ACTIV-5 (Big Effect Trial): 11 sites open; (b) (4) as of 02/03
 - Sample size (patients per arm): 100
 - Prioritizing additional investigational agents

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

- The ACTIV team believes there is a lot of evidence the outpatient setting with the monoclonal antibodies that if we can pull data from our (b) (4) studies that there may be enough data to show correlation between virologic and symptomatic endpoint and change practice
- Bill Erhardt: Vaccine post mAb coordination: the ACTIV-2 team has drafted a protocol to look at vaccine immune responses in patients who have received mAb
 - (b) (4) agreed, but there is no availability at (b) (4) for clinical trial labeled vaccines; exploring avenues → may reach out to (b) (4) to see if they have clinical supplies that they can provide; there may also be potential with (b) (4)
- Convalescent Plasma Trials
 - CONTAIN COVID-19 (inpatient)
 - 19 sites open; (b) (4) as of 02/03
 - Sample size (patients per arm): 500
 - DSMB met on 01/22 to review data from the first 715 patients → received a Continue as Planned; next DSMB will be on 02/05
 - Adding up to 10 more sites
 - PassItOnII (inpatient)
 - 23 sites open (adding up to 10 more); (b) (4) as of 02/03
 - Sample size (patients per arm): 500
 - DSMB met on Tuesday, 01/26 to review data from (b) (4); received a Continue as Planned; next DSMB to review (b) (4) analysis is mid-March
 - Rationale and design manuscript almost ready for submission/ final comments being reconciled
 - Sarah Dunsmore: manuscript should be submitted this week; all sites are sending in their final comments and they are being reconciled by the coordinating center
 - Meta-analysis: All three protocols have been with the FDA's statisticians; Sarah will reach out after Friday to see where it is
 - **SHOUT OUT to Will Bailey on being able to find the blinding placebo!! 😊 He obtained (b) (4) for blinding placebo solution from (b) (4)!
 - **Protocols and statistical analysis plans from the three USG hospitalized patient clinical trials (CONTAIN COVID-19 and PassItOnII, VA_CURES) provided to FDA statisticians for continued development of hospitalized patient convalescent plasma meta-analysis.
 - **Road to the Plasma Summit – (b) (4) is set for February 8; (b) (4) samples to be analyzed by (b) (4) – readout expected in late February.
 - C3PO (outpatient)
 - 51 sites released to enroll (2 on hold); (b) (4) as of 02/03
 - Sample size (patients per arm): 450
 - Working with 65 sites to get them open

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

- DSMB met on Tuesday, 01/19 to review first interim analysis for efficacy and futility on 300 patients (sample size increased – will figure out what the expanded enrollment looks like for this trial) → recommendation to continue; next DSMB meeting is planned for 01/25 for 2nd interim analysis on 450 patients
- Perhaps need to start collating information and have a template for the individuals on the operations side to look at and reference
- Sarah Dunsmore: vaccination has been an issue for all trials in different ways; it has become an issue as participants are asking to unblind for vaccination purposes

Call Center Update

(Chris Shreeve, HHS)

- Slight dip from 25 calls (1/18-1/24) to 22 calls (1/25-1/31) to the general line, but the overall trend is going up
- Visits to the CombatCOVID website: last week → 47,500; this week → almost 88,000 – large surge!
 - Best referrals coming from the paid search
 - HHS Lilly social media campaign is also driving people to the mAb page on the CombatCOVID website
 - [mlmclinicaltrials.gov](https://www.clinicaltrials.gov) > CDC in the last two weeks for referrals
- Starting focus groups next week to hone in on messaging for CombatCOVID (Twitter, Facebook, Instagram)
- Working on changing a flipbook into a video
- Not yet tracking referrals for click-throughs to different ACTIV studies – would like to do this to better assess the effectiveness of the CombatCOVID program on the ACTIV studies
- 7% of the COMBATCovid users are healthcare providers

Operational Challenges with Multiple Routes of Administration

(Stacey Adam, FNHI)

- Discussion on some lessons learned that we can take out of some choices that were made early on by the Agent Selection and Prioritization Committee
 - Is the agent right for the target population?
 - Does it fit well with the overall kind of administration and cadence of the study?
 - Routes of administration that have presented a bit more of a logistical challenge and (in the case of ACTIV-1) may even be causing some recruitment challenges?
- Jane Atkinson (ACTIV-1):
 - There are two IV agents and both of those agents in ACTIV-1 are approved for other uses; patients are given one dose and the day of or the day after randomization; there is also CVC that is 28 days total, twice a day – people that are approached do not want to take oral agents and keep a log after they're discharged from the hospital, so patients are refusing this
 - Another problem is that once somebody is intubated, IV is a much easier way to administer drugs; since there are competing trials, doctors prefer other trials because the route of

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

administration is easier; also CVC presents another issue in that it interacts with other meds

- Difficulty monitoring compliance/ implementation with oral drug (e.g., taking back the empty bottle once the patient has taken all the pills)
- Bill Erhardt (ACTIV-2):
 - No experience with multiple routes of administration yet (only IV for now); however, it appears that ACTIV-2 will probably run into the same issues as ACTIV-1 → oral and inhaled agents are coming up into ACTIV-2
 - Multi-hour intravenous infusion in an outpatient setting resulted in slow ramp-up for this study

Cross-Trial Operations Meeting: Going Forward (Stacey Adam, FNIH and Kevin Bugin, USG Pandemic Response)

- Conversation around the cadence and timing of these meetings because there seems to be some attrition
- Bi-weekly seems to be the right cadence for this meeting going forward; however, we need to make sure that a representative from each ACTIV team is present
- Best to stagger this meeting so that it is not on the same week as the larger meeting on Friday

*****REMINDER: Around the biospecimen prioritization efforts → please have a team member take a look at the (2) slides comparing the language in the ICFs and looking at the sample collections and what might be there as a remaining sample – please give us feedback***

CHAT

- **Libby Higgs**19:48
On the G7 meeting this am, Canada held up the cooperation on the trials on ACTIV 4a as a positive exemplar.
- **Deydre Teyhen**20:06
Greats news!!!
- **Bill Erhardt**20:27
Very nice to see the positive recognition. All of these trials are amazing and should be recognized.
- **Libby Higgs**21:33
Yes, the focus of the G7 is around what we can do to enhance collaboration on clinical trials focussed on therapeutics. I did outline the ACTIV program as the USG integrated prioritized research agenda.
- **Libby Higgs**21:54
Also focusing on sharing reagents, viruses, etc. tech transfer issues
- **(b) (6)** 13
It is a great lesson learned, and excellent example of research collaboration. Mentioned now in several discussion papers. Milken Institute's paper also gave a nice shout out to ACTIV.
https://milkeninstitute.org/sites/default/files/reports-pdf/MI_SilverLining_012521.pdf
- **Stacey Adam**24:37
Thanks, Kevin!
- **Libby Higgs**24:52
Appreciate the paper Kevin. thanks

ACTIV, Cross-Trial Operations Meeting

Thursday, February 4th, 2021

- (b) (6) 38:04
Do we think it would matter if a pt received low titer vs high titer CCP wrt vaccine efficacy?
- Sarah Dunsmore 40:04
(b) (6) - not sure if there is any evidence on low titer vs high titer CCP and vaccine efficacy. The trial I mentioned (b) (4) only uses high titer CCP.
- (b) (6) 41:07
Thanks, Sarah.
- Sarah Dunsmore 43:41
Vaccination also effects the CCP donor pipeline. Current guidelines suggest not accepting CCP donations from vaccine recipients because of the unknown nature of antibody profiles.
- Libby Higgs 58:08
Agree with Biweekly
- Sarah Dunsmore 58:23
Agree with Biweekly
- Cynthia Boucher 58:28
Agree w/ Biweekly
- Bill Erhardt 58:34
Agree as well. Would also suggest that one of the off weeks is the week that we have the Friday full team meeting.

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) Co-Chairs briefed other WG members on their May 6 presentation to the ACTIV Leadership Group. The WG then discussed progress of its current activities and suggested potential new directions, including requesting support from the Leadership Group (especially from federal partners) to catalogue all other COVID-19 clinical trial efforts worldwide to help inform this WG's strategic decisions. WG members also proposed launching a master protocol designed specifically for head-to-head comparisons of SARS-CoV-2-specific monoclonal antibodies.

WG Co-Chairs' Presentation to ACTIV Leadership

Yesterday, Drs. Eric Hughes and Sarah Read (WG Co-Chairs) presented to the ACTIV Leadership Group the TX-Clinical WG's current progress and upcoming plans. The Leadership Group praised the WG for its rapid completion of Wave 1 agent prioritization (i.e., for ACTT-3 drug repurposing clinical trials) and agreed with its hybrid approach to developing master protocols for (1) rapid testing of repurposed compounds in hospitalized patients, including its decision to test prioritized immunomodulators and anticoagulants under separate master protocols, and (2) more comprehensive testing of Phase II-to-Phase III agents targeting more varied patient populations (i.e., ambulatory patients and unaffected individuals) under a *De Novo* 'Gold Standard' master protocol. Drs. Hughes and Read also reported that the TX-Clinical WG aims to incorporate existing trials of both (b) (4) (ACTT-2) and Hyperimmune Intravenous Immunoglobulin (hIVIG) (INSIGHT: Protocol 12) into ACTIV's master protocol portfolio to support comparability of outcomes across these various agent classes.

Drs. Hughes and Read's responses to the Leadership Group's questions are summarized below.

Selection of (b) (4) for Testing

Dr. (b) (4), (b) (6) expressed surprise at the APC's selection of (b) (4)—whose mechanism of action is (b) (4)—given how often this drug class has failed in clinical studies for other indications, suggesting that this agent class holds no biological relevance for humans. The Co-Chairs explained that (b) (4) are elevated in ARDS patients, and that (b) (4) is not yet being studied by other researchers despite its availability and promising safety profile.

Standardization of Time to Recovery

To support standardization of time to recovery as a primary endpoint across master protocols, the TX-Clinical WG is currently evaluating the ordinal scale or a defined dichotomous scale as an endpoint measure.

Limited Availability of (b) (4)

Although the TX-Clinical WG cannot guarantee adequate supplies of (b) (4) to execute its proposed ACTT-3 master protocol, Dr. Janet Woodcock from the Food and Drug Administration (FDA) confirmed that FDA can assist in obtaining an adequate supply for ACTIV trials.

U.S. Department of Veterans Affairs Master Protocol Efforts

Dr. Rachel Ramoni of the United States Department of Veterans Affairs (VA) informed WG Co-Chairs about ongoing VA efforts to develop master protocols for COVID-19 clinical trials. VA is eager to collaborate with ACTIV and would be interested in potentially aligning endpoints with ACTIV's master protocols to support data integration and comparability. [Post Meeting Note: TX-Clinical Co-Chairs met with VA about their master protocol and they are interested in aligning endpoints and synergizing the process, currently the agent selected for their trial does not conflict with those that ACTIV has selected.]

Master Protocol for SARS-CoV-2 Monoclonal Antibodies

During Co-Chairs' May 6 presentation, the Leadership Group also asked whether the TX-Clinical WG had considered prioritizing SARS-CoV-2 monoclonal antibodies for ACTIV clinical trials. Drs. Hughes and Read relayed that the Agent Prioritization Committee (APC) eliminated monoclonal antibodies during Wave 1 triage because of their early stage of development and clarified that the APC will reconsider these agents during future waves for testing under the *De Novo* master protocol. However, during today's meeting company representatives noted that many industry partners are planning to start trials of their monoclonal antibodies in mid-June, which may precede ACTIV's *De Novo* protocol and leave these agents unavailable for ACTIV testing.

Several WG members during today's meeting expressed a strong desire to establish a separate master protocol exclusively for testing all candidate SARS-CoV-2-specific monoclonal antibodies in a head-to-head comparison. Dr. Keith Gottesdiener suggested that high-ranking government officials within ACTIV release a joint call to pharmaceutical companies that possess such agents encouraging them to submit their monoclonal antibodies for these head-to-head comparisons in adaptive clinical trials (i.e., enabling the most promising agents to advance rapidly while less promising agents are either slowed or removed). The WG's company representatives reported that their respective companies would likely be willing to provide their monoclonal antibodies for these studies.

Request for ACTIV Leadership Group Support

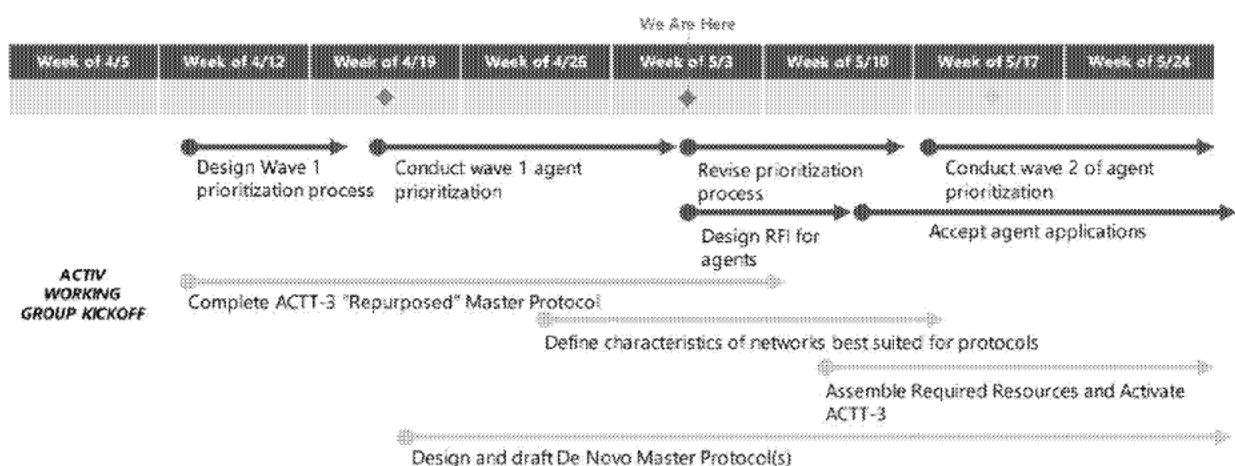
TX-Clinical WG members discussed existing efforts outside of ACTIV to coordinate clinical trial networks or run multi-agent clinical trials across patient populations for efficacy against COVID-19. Such efforts include a 'network of networks' being organized and led by the National Heart, Lung, and Blood Institute (NHLBI) and programs of individual pharmaceutical companies, as well as other efforts by governments, companies, and research institutions around the world. Dr. Adam notes that the NHLBI effort was in discussion become part of ACTIV and would likely do so.

WG members generally agreed that its strategic decision-making should be informed by a fuller understanding of what other efforts are taking place, including who is leading them, what their objectives are, and how much progress they have made. Without understanding the landscape of COVID-19 clinical trial and especially master protocol efforts around the globe, the TX-Clinical WG cannot design a strategy to fill gaps in that landscape and thereby ensure it adds maximum value. Dr. Peter Stein initially proposed establishing an additional 'Intelligence Subgroup' to

assemble intelligence on all other COVID-19 clinical trial efforts worldwide. However, WG members eventually agreed that ACTIV Leadership should be responsible for providing this information to the WG to support its work. Specifically, top government officials and a subset of prominent Chief Executive Officers from pharmaceutical companies should solicit information from organizations to create a landscape assessment of existing efforts and define a high-level, holistic strategy for ACTIV; all WGs can then refer to that overarching strategy when making more granular strategic decisions.

Anticipated Timelines for Upcoming WG Activities

The WG reviewed the updated timeline below, with the APC activities colored blue and Master Protocol Subgroup activities colored green. Arrows extending beyond the right-side edge of the table indicate activities that will continue past the end of May.



Participants noted that the anticipated timeline for revising the agent prioritization process and collecting all data needed to evaluate Wave 2 agents, and for completing Wave 2 prioritization, may be too compact (i.e., this process may need to extend beyond the end of May). Dr. Stacey Adam acknowledged this possibility but explained that this timeline reflects the anticipated launch of the *De Novo* master protocol by the end of June (i.e., Dr. Adam created this timeline to allow the Master Protocol Subgroup to know which agents were prioritized during Wave 2 when it begins to design its *De Novo* protocol during June).

Next Steps

Dr. Gottesdiener will draft a short statement from the TX-Clinical WG directed toward the ACTIV Leadership Group requesting its support in assessing the overall landscape of existing COVID-19 master protocol efforts worldwide, and in establishing an overarching strategic vision that can guide the various WGs' more granular strategic decisions. He will circulate this draft to Drs. Judith Currier, Elizabeth (Libby) Higgs, Amanda Peppercorn, Carl Garner, and Peter Stein for an initial review, and will then provide it to Dr. Adam and the co-chairs for review. The overall TX-Clinical WG will then review the statement before submitting it to the ACTIV Leadership Group for consideration.

Dr. Currier also suggested that the APC maintain a running list of agents eliminated from triage because they are already being studied to ensure that the APC does not waste time rereviewing agents that should not be tested by ACTIV. Dr. Joan Butterson requested that leaders from the AIDS Clinical Trials Group (ACTG) be invited to present their ambulatory master protocol design. Dr. Adam will contact ACTG representatives to schedule this presentation. [Post Meeting Note: The ACTG Network will present to the Master Protocol Subgroup on Monday, May 11.]

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

(b) (6) 16:18

Perhaps I should know this, but how well are we aligned with the ACTT1 and ACTT2 teams?

(b) (6) 41:55

I agree with the last comments - we need to get our heads around and hopefully consolidate the various master protocol efforts!

(b) (6) 49:35

I plan to discuss this with my center director, chris austin

High-Level Meeting Summary

The Agent Prioritization Committee (APC) of the Clinical Therapeutics Working Group (TX-Clinical WG) reviewed the recommendation of (b) (4) for Wave 1 prioritization. The group also discussed optimization of the scoring process for future prioritization waves, focusing on modification of key prioritization criteria, particularly for antiviral candidates; differential weighting of criteria; and interpretation of criteria. Prior to the scheduled agenda, members of the APC briefly discussed the Gates Foundation's ReFRAME effort.

A summary of key discussion points follows.

ReFRAME Screening Data

Prior to the meeting, the group revisited its discussion of the Gates Foundation's ReFRAME antiviral screening effort. Dr. Ruxandra Draghia-Akli highlighted findings on synergy versus antagonism between antiviral drugs. Members of the APC expressed continued interest in methods used by ReFRAME to select its top compounds, in particular whether ReFRAME screening focused on mechanism or structure for candidate antivirals.

Review of (b) (4) for Wave 1 Prioritization

The ACTIV Leadership Group raised some questions about the APC's recommendation of (b) (4); for Wave 1 prioritization. Based on this feedback, the APC reexamined their recommendation. Some participants agreed that (b) (4) could benefit from additional small trials to validate evidence of a signal, particularly given prior failures of (b) (4). Other participants disagreed, noting a strong rationale for the use of (b) (4) to treat SARS-CoV-2. Dr. John Mellors highlighted a recent report on (b) (4), that supported blocking the (b) (4). In this single-arm trial, (b) (4).

(b) (4) Although the mechanism(s) controlling viremia remained unclear, the data were compelling. Dr. Keith Gottesdiener offered to distribute additional information on the potential mechanism of (b) (4) to the APC. Dr. Gottesdiener also offered to contact (b) (4).

Process Improvements for Future Prioritization Waves

Following the conclusion of Wave 1 agent prioritization, the APC offered five high-level recommendations to optimize the prioritization process: (1) improve data assembly, (2) amend scoring criteria, (3) assign differential weights to scoring criteria, (4) clarify interpretation of scoring criteria, and (5) recruit additional expertise, especially during triage.

Data Assembly

To ensure reviewers' access to consistent data for all candidate agents, Dr. Stacey Adam outlined a two-pronged approach to improve data assembly: (1) enhance available data during triage and (2) increase the time between triage and scoring in order to assemble one-page data

packages for each agent that passes initial triage. The data packages will likely be modeled after an R&D Consortium informational sheet provided for one agent during Wave 1. Alternatively, data could be solicited directly from each drug manufacturer; however, concerns with this approach include the availability of compiled data across multiple sites and the ability to acquire data in a timely manner. Dr. Adam also outlined efforts to increase communication with the ACTIV Preclinical Therapeutics WG and the Gates Foundation, as well as ongoing work to resolve confidentiality issues preventing data sharing from TransNIH Data sharing efforts.

Modifications to Scoring Criteria

Participants agreed that more objective criteria would facilitate the triage process, particularly for antiviral candidates. They focused on amending three key criteria for scoring post-triage: “rationale for mechanism of action (MOA)”, “SARS-CoV-2 trials”, and “preclinical data.”

Rationale for MOA

The APC agreed that a strong rationale alone, without additional supporting preclinical or clinical data, should not be sufficient to prioritize an antiviral candidate for ACTIV clinical trials. Participants also discussed expanding rationale evaluation to include proof of target engagement using a SARS-CoV-2-relevant measure.

Preclinical Data

Members identified the critical preclinical data necessary for robust evaluation of antiviral agents: (1) molecular target; (2) EC50 (protein-adjusted, if available); (3) PK/PD; (4) toxicity/maximum tolerated dose; (5) peak-to-trough plasma ratios; (6) half-life; and (7) clinical stage. Where more than one assay has been performed for an agent, an inventory with clear conditions on assay performance would add quality to the baseline evaluation data.

SARS-CoV-2 Trials

The APC agreed on the need to define an appropriate reference population (e.g., critical care patients) when evaluating clinical data. While some members felt that data from uncontrolled clinical trials should be included only if the data indicated drug action on a relevant pharmacokinetic endpoint, other members thought demonstration of clinical improvement in a case series was sufficient. Dr. Walter Koroshetz recommended gathering information on biomarkers and biological measures relevant to SARS-CoV-2 to support further evaluation of candidate agents.

Differential Weighting of Scoring Criteria

For antiviral candidates, the APC generally agreed that greater emphasis should be placed on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK/PD) compared to safety (except for significant concerns), drug-drug interactions, and availability/scalability. However, they agreed that more heavily weighting the first three criteria may not adequately resolve scoring difficulties noted during Wave 1 prioritization, particularly for antiviral agents. Therefore, members suggested a *staged approach* to scoring: candidate agents would undergo

a second triage step based on scores for rationale for MOA, SARS-CoV-2 trials, and preclinical data. Second-stage criteria (i.e., safety, drug-drug interactions, and availability/scalability) would be scored only for those agents that passed the second triage. The APC agreed that the second-stage criteria are irrelevant if candidates lack a strong rationale and supporting data. Thus, the staged approach ensures that only candidates with a strong rationale and supporting preclinical or clinical data are prioritized.

Dr. Naimish Patel noted the “rationale” criterion was not always discriminatory for the immunomodulatory agents. Instead, he favored compounds with clinical data. Dr. Higgs pointed out that the staged approach would allow rationale and clinical data to be evaluated together for immunomodulators, as well.

Dr. Michael Vincent expressed concern about compartmentalizing the “safety” and “rationale” criteria in different stages. He emphasized the importance of clinical context when considering the safety of compounds, noting safety of a compound may vary in prophylaxis/outpatient populations compared to critical patients. For the critical patient population, it may be difficult to separate safety from rationale.

Interpretation of the “SARS-CoV-2 Trials” Scoring Criterion

The APC identified two broad ways to interpret the “SARS-CoV-2 Trials” criterion: (1) the existence of *ongoing* phase III clinical trials for a candidate molecule or another in the same class or (2) the *quality of clinical data* from smaller completed trials (e.g., Phase I or Phase II). Dr. Adam clarified that the clinical trials criterion used at the scoring stage focuses on the validity of data from smaller existing trials (e.g., were they single arm, how many subjects were evaluated, how relevant was the data collected to SARS-CoV-2). To avoid duplication of effort, candidate agents are triaged if they, or other molecules in the same class, are being evaluated in other large randomized trials. However, some members felt ongoing clinical trials should be revisited during the scoring step.

Next Steps

Dr. Adam will generate a mock revised scoring framework based on feedback from the APC, including differential weighting for key criteria and consideration of a sequential or staged scoring process post-triage. Approaches to acquiring data for candidate agents and recruiting additional expertise for triage will be discussed at the next APC meeting. Dr. Gottesdiener will follow up on the status of ongoing or planned clinical trials with (b) (4)

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Rosa Maria Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

John Mellors to Everyone 00:15:10

Was leronlimab considered?

Walter Koroshetz to Everyone 01:00:55

So maybe the SARS-COV-2 trials should be changed to " Proof of principle data from SARS-COV-2 trials".

Stacey Adam to Everyone 01:01:13

Thanks, Walter.

John Mellors to Everyone 01:02:36

I like that. Proof of principle or suggestive in vivo activity?

Walter Koroshetz to Everyone 01:04:31

Maybe segment the population and match the drugs to the patient group?? ICU or not.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Statistical Sub Team Meeting, Key Takeaways

Wednesday, May 6th, 2020

Action Items

Action Items		
	Information	POC
1	Share resources • ACTT-2 table of recoveries / ACTT-3 sample size calculations • Danyu statistical appendix	Lisa LaVange, Mike Proschan
2	Provide outline of simulations and have options ready by Friday, 5/8	Sandeep Menon, Mike Proschan, Pranab Ghosh, Christophe Le Corre
3	Regroup on Saturday	Full Statistical Sub Working Group

Key Takeaways

- 3 drugs, 1.25 rate of recovery, non-binding futility.
- No strong control, will make sure that the interim is controlled
- We will come up with simulations where we will play with both the efficacy and futility boundaries.
 - Will come up with multiple options to come with an aggressive futility, something milder, or a light futility rule.
 - Based on conditional power but will reverse translate futility into the effect size
- For each pair-wise comparison, 2-tailed, 5 %
- Aiming for a double-blind trial: one placebo injection and one placebo pill
- Further discussion needed on how much is our inflation of Type 1 error?
- Suggestion to use terminology alternative to family-wise error

Opening

- Lisa LaVange, Sandeep Menon, and Mike Proschan have been spearheading the statistical work within our Sub Group.
- Christophe Le Corre and Pranab Ghosh will be helping with the simulations that (b) (4) has kindly agreed to help ACTIV with.
- Lisa LaVange:
 - It seems like every meeting, we keep wanting to come back to wanting to weed out drugs earlier. We're back to focusing on immunotherapies. We still have to deal with anticoagulant treatments. Even with 3, possibly 4 drugs, the sample sizes can get big if we follow the ACTT protocol: ~ 1500 people.
 - Rate of recovery – I think we are back to 1.25. We want something aggressive.
 - WG members really want to see simulations.

Wednesday, May 6th, 2020

- Mike Proshan
 - Not sure if we want to use conditional power rule where the threshold we use changes with time because later, the triangular rules that make it so that your futility boundary actually gets closer and closer to your efficacy boundary as the trial progresses – that's a really aggressive futility rule. Don't know that we want to be that aggressive.
 - The other question is do we want to have a binding futility rule, which Lisa in the past has expressed a concern about.
 - There are some MAMS (multi-arm, multi-stage) designs that propose different futility stopping guidelines. We could use some of those as well.
- Sandeep Menon
 - On board with most of what Mike said. Got the first author of the MAMS design to work with us. Agree on the conditional power that changes with the time. Clinicians don't usually appreciate conditional power, but if we can convert that to an effect size – say, we are walking away if our lower bound is, for example, 10% of effect size – they understand that better and it's easier to relate.
 - We can start with conditional power, but in terms of communication, we can go back to treatment effect that would be helpful.
 - We should go with non-binding futility. This means we're not stuck with a binding futility rule.
 - In terms of the MAMS, need to think whether group sequence with two stages is good enough or make more sophisticated using MAMS design. Helps with flexibility A vs. SoC, B vs. SoC, and covered with the strong control. Don't know if we want to make it that sophisticated.
- Lisa LaVange
 - Agree with Sandeep on effect size – it's the easiest way to get people to understand what they'd be leaving on the table. If the null is wrong, alternative is true, and we really have time to recovery of 25%, the chances we'll leave one of these on the table is x. And we'd take it down from there and say if it's 1.35, we probably won't leave it on the table. That helped me get people to make decisions about conditional power.
 - The other thing I kept running into: in this same scenario, we started with 6 drugs, and people kept wanting to rank the drugs. We did simulations with that.
 - In our case, it might be starting with the top 3 and taking the top 1.
- Sandeep
 - We can do that, but it's complicated statistically. It may become too complicated than we want to make in this trial.
 - It'd be easier if you're going from 5 or 6 comparisons, for example, and we can have futility or even efficacy rules in terms of what to proceed with – maybe 3 or 2 combinations that we can think about taking to the next stage.

Wednesday, May 6th, 2020

- We can have the combination approach to tie this up using sines approach or gatekeeping.
- Lisa LaVange
 - Not worried. We're dropping a drug, not a dose – it's like a mini trial.
 - Know that we'd talked about with Mike that if we have 4-5 drugs, would need multiplicity control. Other than that, we're stopping a sub trial.
- Mike Proschan
 - Thought we had decided that since there's only going to be 2 other arms (or is it 3 now?) – we'd decided that we probably wouldn't need to do a multiplicity adjustment in that situation. I don't know for sure if the FDA is on board with that, but I wouldn't be surprised if they thought that was okay in this situation.
- Lisa LaVange
 - I think they were okay with it.
- Michael Proschan
 - Otherwise we need to increase the sample size even larger
- Sandeep Menon
 - Agree – it would be too complicated
- Lisa laVange
 - Agreement that we don't worry so much about non-binding futility? We'll ultimately need to get the FDA to weigh in.
- Michael Proschan
 - When we say "not to worry too much," we're saying that we'll go with a non-binding futility rule, correct? I would completely support that. In general, binding futility rules, especially if they're used to change the upper boundary – which we're not doing here – that's troubling. Some judgment is always involved
- Lisa LaVange
 - If there was ever a scenario where you had to rely on judgment, it's this one because there are so many trials and results, so many things changing.
 - Fascinating to read RECOVERY paragraph about the DSMC because they basically said the DSMC will tell them what to do. They had the Dunn's multiplied comparison test.
 - From being inside the FDA – (b) (5)
[REDACTED]
 - Do we want to go back to the MAMS?
- Sandeep Menon
 - So, currently we're thinking about 3 arms vs. SoC, and whether we need to go to for a full-blown MAMS or water it down a little bit if possible?

Wednesday, May 6th, 2020

- If you're thinking about 2 stages of design – 1 for futility early and possibly later, 33% and 67%...
- Pranab Ghosh
 - Is the purpose of futility – drop ineffective arms or to stop the trial early?
- Sandeep Menon
 - Ineffective arms so far. We hope some not all of the arms are meeting the futility. If all arms are meeting the futility, we will stop.
- Lisa LaVange
 - But arm isn't usual arm. This isn't a factorial. Think about each of the trials as a sub trial. We're not comparing drugs to each other.
 - We've got 3 drugs, 3 comparisons: A vs. control, B vs. control C vs. control. And we want the futility of each drug vs. control. We will share controls as much as we can. They'll be concurrent, but right now, we think we'll start to study with all three drugs. There's a chance we could start with 2 and add a third or fourth later, and we'll probably have to look at which controls we use. The simplest is that we start with 3 drugs ready to go; everyone gets a common control; we don't know about blinding yet.
 - Yesterday [during the Master Protocol Sub Group meeting], it sounded like we maybe could have a double-blind trial: one placebo injection and one placebo pill.
 - If we get double blind, then don't have to worry so much about endpoint and subjectivity of endpoint. That would be terrific.
- Pranab Ghosh
 - Think MAMS will be less powerful than doing it separately. Don't think you have multiplicity adjustment issue here.
- Sandeep Menon
 - We need to think about how much is our inflation of Type 1 error.
 - Doing a back of the envelop testing:
 - We're trying to do 2 interim analyses. We're assuming 3 arms vs. SoC. So, in the first interim, we'd do 3 tests, and then in the second interim, another 3 tests.
 - My back of the envelop calculation – the type 1 error if we don't correct for anything would be 10-12%.
- Mike Proshan
 - We have to correct for interim analyses; we were talking about not correcting for the arms, the multiples.
- Lisa LaVange

Wednesday, May 6th, 2020

- It's as if we correct for interim analysis for 1 drug. Don't think about this as 3 tests at interim. It's like drug A gets own alpha, drug B gets own alpha, and drug C gets its own alpha.
- For drug A, we have 2 and have to correct for those 2 interims; and B you have to start over with a new alpha. So, it's like 3 little trials inside a new network.
- We're doing a pair-wise control, not a family-wise control.
- Pranab Ghosh
 - We have some flexibility with that. With pair-wise control, we'll have some amount of independence.
- Lisa LaVange
 - We mentioned yesterday [during the Master Protocol Sub Group meeting] that we don't have to do the 33% on interim on everyone at the same time.
 - People thought that operationally for the clinics and coordinating center, it would be too complicated, and we should just say that 33% of the people enrolled will go. 33% would be about 650. So, when 650+ people enroll, then we'll look at futility for each of the 3 trials but just look at as separate trials.
- Pranab Ghosh
 - Suppose at interim, you decide to stop 1 of futility. Will you redistribute the patients that were supposed to enter? If some patients didn't enroll yet at time of interim analysis, what will you do with remaining patients?
 - Supposing you drop some arms – due to dropping an arm early, you can possibly increase sample size on remaining arm.
- Lisa LaVange
 - We'd start with 1:1:1:1 randomization, and then it becomes 1:1:1.
 - It's only 28 days.
 - Assume we would lower overall sample size, not increase. Our target is based on number of recoveries, multiplied up for drugs. We would lower the sample size. That was the bargain we made yesterday that we'd go for the 1.25 instead of the 1.30 or 1.35 for our power, which takes us from 1400 to nearly 2000 patients. But in return, we'd stop early and lower that sample size.
- Sandeep Menon
 - To summarize:
 - No strong control, we'll make sure that the interim is controlled
 - We'll start with the hazard ratio of 1.25 and have a non-binding futility and come up with simulations where we will play with both the efficacy and futility boundaries.

Wednesday, May 6th, 2020

- We'll come up with multiple options to come with an aggressive futility or something milder or a light futility rule, so we can distinguish that.
- Then we'll try to make sure that even though it'll be based on conditional power, we'll reverse translate futility into the effect size, so we're on the same page.
- Would like to suggest from perspective of Type 1 error control – we should know if we've done a trial with all the controls, how much is our inflation? This would be more of an academic exercise but want to make sure we can at least show it to the FDA that we're maybe have 3% or 5% inflation.
- Mike Proschan
 - I had done some calculations using a Dunn's calculation where instead of controlling family-wise error rate at 5% two-tailed, I looked at controlling at 5% one-tailed, how much would you have to increase critical value. I did not take monitoring into account, but based on that simple calculation, I believe you have to increase the critical value from 1.96 to 2.06. So, it's not a big increase to get it to at least a one-sided family-wise error rate of 5%.
- Lisa LaVange
 - Sandeep, keep in mind this trial is not exactly the master protocol like I-SPY. At least that the high-level part of FDA (b) (5) [REDACTED]
 - If you put family-wise error on top of that, you defeat the motivation. Right now, if each of these 3 drugs were testing, there would be no family-wise control. It goes against why FDA is behind the master protocols.
- Mike LaVange
 - It is helpful to know what the family-wise error rate is though. It'll be reassuring to see that it's not ~ 30%.
- Sandeep Menon
 - Is thinking 6 months down the line. If we've done the exercise, we know what the risk is. Things may change.
- Lisa LaVange
 - Outside of our group, let's not talk about this as family-wise error. We may end up with multiple primary endpoints. Don't know that we'll end up with time to recovery at the end of the day.
 - We should call family-wise error something else for political reasons.
- Mike Proschan
 - Terminology is important.
- Sandeep Menon

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Statistical Sub Team Meeting, Key Takeaways

Wednesday, May 6th, 2020

- We can take this framework, play around with simulations, and come back with some numbers.
- Lisa LaVange
 - We picked up the 33% and 67% because it's even division, but should we look at 25/50/75?
- Mike Proschan
 - Good question. We didn't do well at even having two interim, but I agree that if you do have 4, you have the potential to drop earlier and save more sample size.
- Lisa LaVange
 - We're up near 2000, so 4 would be after the first 500. Like the idea of looking at 500 and 1000 and not waiting for 700-800.
- Mike and Sandeep agreement on this
- Sandeep Menon
 - Agree, given the urgency. We can even add 3 and add one more based on information time. Information time will drive this.
- Lisa LaVange
 - And then, the other parameters: under the null, the (b) (4), (b) (5) recovery rate in ACTT1 which is 73%. The number of recoveries is still the same as the draft protocol. So, if we go for 1.25, the number would be 723. 723 for each pairwise comparison, if you divide that by .73, you get 990 patients. For 3 drugs, you double it because they share controls.
- Sarah Read
 - Confirms that there will not be a fourth drug.
- Sandeep Menon
 - Will we power based on primary endpoint, which is time to recovery? Confirming this.
- Lisa LaVange
 - Yes
- Sandeep Menon
 - Asking Mike for assumptions he made initially for coming up with 2000 subjects. If we're doing survival endpoint technically here, we still need to know study duration and possibly also the recruitment rate to enter into simulations.
 - Pranab confirms.
- Lisa LaVange
 - Started editing ACTT-3 based on ACTT-2. Power section is what Sandeep needs. Send to Sandeep.
- Sandeep Menon

Wednesday, May 6th, 2020

- That assumes no interim looks, right? The power calculation because depending on if you add interim looks the average sample size goes up.
- Mike Proschan
 - We were using the O'Brien and Fleming, so the inflation of the sample size is very small to account for the interim analysis.
- Lisa LaVange
 - Mike, the number of the 732 recoveries was including O'Brien and Fleming?
- Mike Proschan
 - No, it was not. But if we're going to experiment with different group sequential monitoring boundaries like something more aggressive, then we'd need to take that into consideration because that would increase the sample size.
- Lisa LaVange
 - Sandeep should look at ACTT-3 sample size calculations.
 - Sample size is based on the recovery. Sandeep's calculations will be run on recoveries, not on people.
 - Those recoveries are for a pair. So, it's 1 drug. We don't triple it for 3 drugs because you're sharing the placebo.
- Mike Proschan
 - Yes, so you need roughly 723 divided by 2 recoveries in each arm, and then you have the 3 actives and 1 control. So, that's where Lisa was multiplying by 2. Because we take 723 over 2 and multiply by 4 = number of recoveries. Then you divide the result by .73 to get the number of people.
- Sandeep Menon
 - Makes sense. We may need to fine tune depending on what boundary we use and how much will be inflation.
 - Will also start with O'Brien and Fleming
 - Hope to get aligned by this weekend with his stats sub group
- Christophe Le Corre
 - Do we expect the same level of efficacy for the 3 comparisons?
- Lisa LaVange
 - Don't know, but we want to power to the same.
- Mike Proschan
 - The calculation that we did where we divided by 2, multiplied by 4, etc. is an approximate answer. If the treatment is really good, then there will be more recoveries in that arm. So, it won't be quite as simplified as we made it, but I don't think it'll be very different from that. It will be close.

Wednesday, May 6th, 2020

- Christophe Le Corre
 - Will be good to have non-binding futility because if one arm is much better than the others, it'll be important.
- Mike Proschan
 - Your decision to drop an arm presumably would be guided by what's in the other arms. If you have something that's doing well, might be more likely to drop. If everything is sort of mediocre, you might make a different decision. There are all types of factors that will enter in to whether to drop an arm.
- Lisa LaVange
 - We have ordered secondaries
 - Lisa and Mike discussion on Danyu's paper.
 - Share with Sandeep – Danyu has an appendix where it says to make sure every trial collects the scale, and someone can always put it together with the metanalysis with TSS. He was also saying don't look at mortality; look at time to critical illness. There's a statistical appendix about combining two endpoints in a single z-statistic. I'm not sure if we ever did want to put mortality in, but it seemed like it had relevance to two of our endpoints. There might be a way to put them in to a single test.
- Sandeep Menon
 - We are sure that we want 33%, 67% or 25%, 50%, 75% for the interim analysis, right?
- Lisa LaVange
 - Suggesting 25% and 50% for futility and last one for efficacy
 - Think that the first one being at 500 people will be very popular in case recruitment is hard
- Pranab Ghosh
 - There won't be any efficacy at 25% or 33%?
- Mike Proschan
 - **We want to evaluate two possibilities 33%, 67%**
 - **Other is 25% 50% 75% 100%**
 - **Don't think it hurts to leave the futility rule available at 75%**
 - **Since it is non-binding, we can only approximate what can happen because it'll depend on other factors, but we can't take that into account really because we don't know exactly what will happen.**
 - **Would keep the futility and stopping for efficacy rule in for all of those analyses**
- Sandeep Menon
 - Agree – cleaner, gives flexibility. Start with base case and keep it simple
- Christophe Le Corre

Wednesday, May 6th, 2020

- Futility – how aggressive do we want to be in terms of boundaries and timing? The more aggressive we have, the more impact on the power.
- Sandeep Menon
 - We need to play with the boundaries and come up with options to discuss.
- Lisa LaVange
 - To give a starting point/stopping point possibly. I was able to sell this to a big network before. The true effect is what we powered to, and there was a 15% chance that we'd leave it on the table, but a very tiny (way less than 3-5% chance) that we'd let something bad go forward. The investigators bought it. They were more worried about wasting resources than about leaving something on the table.
- Mike
 - For each pairwise comparison we're looking at two-tailed 5%.
- Next steps:
 - Sandeep and team to have options ready by Friday, 5/8 and group to reconvene this Saturday.

High-Level Meeting Summary

The Agent Prioritization Committee (APC) of the Therapeutics-Clinical Working Group (TX-Clinical WG) debriefed following completion of Wave 1 agent prioritization. Its members reviewed the status of compounds still being assessed in Wave 1, discussed an updated plan for Drug Repurposing trials, suggested process improvements for future prioritization waves, and noted agent prioritization considerations under the *De Novo* master protocol.

Status of Compounds Still Being Assessed in Wave 1

The APC reached final decisions on most compounds in agent prioritization Wave 1 on Sunday, May 3, 2020; it selected (b) (4) to advance to ACTIV's Drug Repurposing clinical trials (b) (4). However, two agents of interest require further consideration: (b) (4). The APC plans to discuss (b) (4) to assist in its evaluation, and a final reviewer is expected to complete evaluation of (b) (4) by the morning of Wednesday, May 6. [Post Meeting Notes: The scores from the (b) (4) to have it included in this round of trials for conduct. However, the team has confirmed with (b) (4) that they have an interest to participate.]

Changes to the Drug Repurposing Master Protocol Plan

The Master Protocol Subgroup of the TX-Clinical WG had originally planned to test every agent prioritized during Wave 1 under an amendment protocol to the National Institute of Allergy and Infectious Diseases (NIAID)'s ACTT2 protocol, which would be called ACTT3. However, details of the ACTT3 design could not be finalized until the final set of prioritized agents was known, so the Master Protocol Subgroup has created a revised plan to test the three immunomodulators and three anticoagulants (and no antivirals) selected. To simplify trial design, the three selected immunomodulators will still be tested under ACTT3, whereas the three selected anticoagulants will be tested under a separate master protocol being developed and led by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Neurological Diseases and Stroke (NINDS).

Process Improvements for Future Prioritization Waves

The APC discussed strengths and weaknesses of Wave 1 prioritization processes and offered suggestions to optimize them for future waves; these suggestions are captured below.

- Reassess the prioritization criteria for each class of drugs to ensure that the criteria are appropriately matched to the class.
- Consider assigning different weights to different prioritization criteria (e.g., potentially weighting criteria differently across agent classes). Ensure that the most relevant criteria drive decision-making.
- Produce a compendium outlining all prioritization criteria with accompanying guidelines for how to interpret and apply them during agent evaluation.

- Ensure that all reviewers are evaluating the same data, and that those data are available in one location to aid efficient, consistent reviews; focus reviews on scientific rationales.
 - For antiviral scoring, it would be useful to tabulate EC50 values to support reviews.
- Allow more time between initial agent triage and final agent prioritization. During this time, ACTIV may (1) contact individual companies to solicit information on compounds to inform prioritization decisions and (2) develop 1-pagers for top candidate agents to assist in prioritization.
 - Participants stressed the importance of identifying appropriate contact persons at drug companies of interest to ensure that data solicitations are received and answered. Although some expressed concern that companies may not respond, Dr. Keith Gottesdiener proposed that lack of response be considered a rule-out criterion to exclude a company's compound from ACTIV testing.
- Involve more appropriate expertise, especially during initial agent triage.
 - Research scientists with close connections to clinical practice could provide useful insights during triage of supportive therapies.
 - Immunologists could assess whether the set of immunomodulators being tested may neglect certain limbs of the immunomodulatory cascade that should be considered.
 - The APC could establish a separate "design and execution committee".
- Follow a sequenced prioritization workflow, wherein each reviewer for each agent class scores agents individually, then convenes with all other reviewers for that agent class to discuss, then allow reviewers to amend their scores, if they feel doing so is warranted based on additional information provided. A process similar to NIH grant review is imagined. Reviewers would then provide these amended scores to the larger APC.
- Consolidate information on existing COVID-19 clinical trials worldwide into an easy-to-navigate platform for reviewers.

Finally, although the APC selected three immunomodulators and three anticoagulants during Wave 1, Dr. Michael Vincent suggested focusing on antiviral agents during future waves, given how many other groups are studying immunomodulators for efficacy against COVID-19.

Prioritizing Agents for Testing under the *De Novo* Master Protocol

Whereas Wave 1 of agent prioritization selected compounds for drug repurposing trials, future waves will select compounds for testing under the ACTIV *De Novo* master protocol. This master protocol is expected to follow a progressive Phase II-to-III design, as opposed to the larger Phase III repurposing design, and this difference could affect agent prioritization criteria.

APC members also highlighted the importance of powering Phase II studies to detect trends in patient outcomes, which can serve as indicators of a compound's potential efficacy and justify advancing that compound to a larger Phase III trial. Members also stressed the potential value of matching therapeutic hypotheses with validated biomarkers to serve as interim endpoints during Phase II trials; such interim endpoints could both improve the efficiency of Phase II trials

(e.g., by enabling Go/No-Go criteria to halt testing of failed agents) and aid prioritization of compounds for Phase III testing.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomaterials Capital; Therapeutic Accelerator Lead, Gates Foundation*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Michael Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

David Wholley, M.Phil, *Senior VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Rosa Maria Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Participants did not use the Zoom chat function during this meeting.

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting 7, Key Takeaways

Tuesday, May 5th, 2020

Action Items

Action Items		
	Information	POC
1	Point of Contact for companies	Stacey Adam/ Ruxandra Draghia-Akli/ Keith Gottesdiener
2	Follow up on process improvement recommendations from the WG: • Reassess and potentially amend the criteria for each of the classes of drugs • Re-evaluate weighting of criteria • Ensure consistency in data being reviewed • More time between selection of final triage list and reviewing final compounds ○ Reach out to companies and get information ○ 1 pager for the top candidates • Document on criteria interpretation • Involve appropriate expertise – potentially have separate ‘design and execution committee • Slightly revised sequencing whereby WG members can score, have an initial score discussion with group, and adjust score. Amended scores come back to larger group.	Sarah Read/ Eric Hughes and Stacey Adam

Key Takeaways

- There was strong encouragement to promote (b) (4) we need to have conversations with (b) (4)
- We have a third reviewer for (b) (4); should know results by tomorrow morning Wednesday, 5/6.
- FC and ACTIV leadership in favor of separating the two groups of therapeutics into a repurposed ACTT-3 and NHLBI-led master protocol
 - Protocol for immunotherapeutic (ACTT-3)
 - Protocol for anticoagulants (NHLBI)
- Suggestions to improve process
 - Libby Higgs:

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group Working Group Meeting 7, Key Takeaways

Tuesday, May 5th, 2020

- For antivirals group, there wasn't enough emphasis for the rationale for the antiviral.
- Too much time spent trying to find data
- Ruxandra Draghia-Akli
 - Scoring criteria much more adapted to antivirals
- Sarah Read
 - More time between creating shortlist after triage and actually doing the scoring to be able to put together information on each of the candidates for review
 - For everyone reviewing antivirals, get them together for discussion before taking to the bigger Agent Prioritization working group
- Keith Gottesdiener
 - Work from common set of data
 - Better when review team members could discuss together and share knowledge
- John Young
 - Agree that valuable to discuss together
 - Antiviral scoring challenge: these are drugs that have been tested, and for many of them, you get widely different EC50 values depending on how the assay is done. It can be like comparing apples and orange even for the same compounds. Having someone get that information and tabulate it for the group would be helpful.
 - (b) (4) For that to come in for second wave temporally makes sense.
- Mike Vincent
 - Immunomodulators – may be good to have relevant experts look at triage list
 - There's so much activity happening outside of this group with regards to immunomodulators. Would feel better about focusing on antivirals
 - If there's a therapeutic hypothesis and biomarker that addresses that therapeutic hypothesis then should be built into study rather than waiting for clinical endpoint.
 - Gathering mechanistic pharmacology data and creating a clearinghouse for this
- Peter Wung
 - Good to have an understanding of options for each category
 - Group 1 and Group 2 immunomodulators groups – slightly different interpretations of the options
 - Suggestion to be aligned on how we interpret the options within each scoring category

Tuesday, May 5th, 2020

- Walter Koroshetz
 - With regard to supportive care group, need more expertise on clinical care side of COVID; people who have really close clinical contact
 - We don't have enough evidence for any of these for a phase 3 trial. Ideally would go into a phase 2 proof of principle trial first. Can we do this in ACTIV? Are there compounds where we can identify a measurement – that if it doesn't meet this bar, will be removed and would be a go/ no go.
 - Is there a conversation that can be had about what measurements would be the go/no go in the phase 2-3?
- Peter Stein
 - Also depends on how confident we are in terms of size of signal
 - Generally, most of the phase 2 trials right now run 200-250 and should be able to see a trend in the right direction and justify going further.
 - Helpful to get more information earlier on about all of the trials globally that are being done, so we have a consolidated place to look at everything
 - Seeing a huge number of immunomodulatory compounds in IND/non-IND; would be helpful to get immunologist view. Are their limbs of immunomodulatory cascade that we're not targeting in current trials?
- Recap and Next Steps
 - Moving forward, likely that drugs selected will go into phase 2-3 progressive design
 - We'll re-look at the criteria for each of the classes of drugs
 - Discuss weighting criteria differently – potentially overall for every class or between classes; make sure that right criteria are carrying brunt of the decision
 - Make sure that we are all reviewing the same data
 - Allow more of a time lag between selection of final triage list and reviewing final compounds
 - This would give us a chance to reach out to the companies and get the information that we need directly from them
 - We can try to put together a 1 pager for the top candidates.
 - Compendium criteria document on how the criteria should be interpreted
 - Involve appropriate expertise – potentially have separate design and execution committee
 - Slightly revised sequencing whereby WG members can score, have an initial score discussion with group, and adjust score. Amended scores come back to larger group.

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group
Ad Hoc Working Group Meeting, Key Takeaways

Tuesday, May 5th, 2020

Action Items

Action Items		
	Information	POC
1	Begin putting together protocol	Lisa LaVange, Sandeep Menon, Mike Proschan, Sarah Read, Eric Hughes, Stacey Adam
2	Simulations	Sandeep Menon
3	Contact drug companies (for IBs and pharmacy manuals)	Stacey Adam
4	Write-up clarifying defining of ordinal numeric endpoints	TBD

Key Takeaways

- The Master Protocol Sub Group agreed to splitting the agents from the Agent Prioritization Subgroup into two master protocols: anticoagulants to the NHLBI/NINDS trial and the immune modulators to the ACTT-3 trial.
- ACTT-3 discussion
 - Draft ACTT-3 protocol is written.
 - Matching placebo will be used if available, enabling a partially masked study. If there are matching placebos for all 3 drugs, will have double-blind study.
 - FDA in general does prefer blinding and strongly suggests blinding when possible.
 - Suggestion to stratify at randomization within sites while continuing to learn from emerging data
 - Understanding that trial would need a strong signal that rises above variations in SoC
 - Suggestions to fix sample size to 1.25.
 - Early aggressive futility looks; frequency and rule TBD
 - Likely drop sample size re-estimation.
 - Start with goal of just under 2000 patient population, with 73% recovery rate for the 3 drugs
 - Questions remaining: how much efficacy is remaining above (b) (4), what are the additive toxicities
- Comprehensive simulation to be conducted
 - Will encompass false positive rates, probability of false stopping, probability of leaving something on the table

Tuesday, May 5th, 2020

- Group needs to determine if we need a bigger sample size. Concern of having a statistically significant trial with a small treatment effect that is not very clinically meaningful.
- Need to more carefully define ordinal numeric endpoints
 - Endpoint “is the patient ready to leave the hospital”
 - “Still needs medical care”

ACTT-3 Discussion

- Uncertainty as to whether we are talking about having a background of full anticoagulation
 - We can dictate what our approach to anticoagulation should be.
 - Just the investigative arms would be full anticoagulation
- Sub Chair – not convinced that anticoagulants are out
 - If you picture ACTT-3 where everyone is on (b) (4) that’s standard of care (SoC) and we’re adding immunotherapies on top of (b) (4). Then do we also add everything onto some type of prophylactic anticoagulant? I thought we don’t have equipoise for that.
 - Do we know enough about therapeutics to put everyone on that, or do we let individual hospitals decide?
- We’re stratifying by site, so assume that everyone at site treated the same.
- Point is to collect information about what people are on to look for interactions.
- Stratifying
 - We can always stratify analysis.
 - If stratifying by site on randomization side, that would be hard.
 - ACTT-1 and ACTT-2 called for stratifying by two level disease severity, and that was it. They multiply quickly.
 - At any given site, think you can be fairly confident that everyone is following same anticoagulant protocol.
 - This would be great benefit to trial of immune modulators if you knew that at single hospital, they are all using single protocol. This may be something we ask hospitals to do and come up with as they enter the trial, so that at least at that site, we know what their plan is. This doesn’t happen naturally. Some hospitals have, but a trial is an opportunity to put some order to the chaos.
 - The initial therapy will not be what the patients end up on in terms of anticoagulation. It’s going to be a moving target as the doctors’ sense of the patients’ risk changes with, say, how the D-Dimer moves. NYU has a protocol for care of patients, and it’s based on the D-Dimer. Doubt that other hospitals do that, but it’s an example. There are changes during course of hospitalization. As they enter ICU, people are more aggressive. Thinking about how to actually understand the interaction between the different thrombotic agents

Tuesday, May 5th, 2020

- people use, how it's changing during course of illness, and how it interacts with immunomodulatory agents seems really complicated because things are changing. As much order to it as possible would be good.
- The R&D consortium has talked to sites, and most sites are developing standards of coagulation. They don't appear to be similar between site and site, but most of them are developing this. These hospitals have 6 ICUs, for example, filled with patients in floors, and it's the wild west; so almost all hospitals have developed. There are dozens of things that change during time that go beyond anticoagulation. We have to pick our questions. We can't control for everything that we want to do. I suggest sites will do their anticoagulation the way they are, and we stratify at randomization within sites and hope that gives us the most chance that everything will come out in a wash while learning from the data.
 - Agreement with this. Don't want to overcomplicate. SoC is SoC. We need to be able to see some effect of these drugs no matter what other things people are on.
- Are we trying to solve too many problems at once?
- If we can discern clear research questions to answer, we can figure out a design.
- We're back to assessing efficacy of 3 treatments, which all happen to be immunotherapies.
 - We'll add them to (b) (4) and take whatever SoC is out there.
 - What we want is a strong signal that will rise above variations in SoC and hope that randomization bails us out from too much confounding.
- Right now, the draft protocol is written. We'll take a matching placebo if we have one. If we do, we can have partially masked study. If there are matching placebos for all 3, we will have double blind study. Not sure when we'll find that out.
- Don't think we'll have time to over-encapsulate anything
 - Oral, IV, subcutaneous – one of each
 - Let's go with open label
 - Still concerned with subjectivity of "still needs medical care" endpoint
- We will continue to revise ACTT-3 with these three drugs
- We did have a blinded SSR (sample size re-estimation) in there after first ~100 patients, and also unblinded SSR using Chen method. This is a placeholder.
- Sandeep Menon not fan of blinded SSR because in this case we have a lot of variability among different combinations, and pooling everything and doing SSR may be a very risky proposition to do in a blinded way.
 - For ACTT-1, the blinded sample size was to check recovery rate. We should know what the recovery rate will be if everyone's getting (b) (4) - we can get that from ACTT-1.
 - It's about 73% at 28 days – on the (b) (4) arm
 - We don't need the sample size estimation for that. We probably can take it out.

Tuesday, May 5th, 2020

- We did keep in SSR based on treatment effects, but this would be different for each drug. We're not pooling these drugs. It's A vs. SoC, B vs. SoC, C vs. SoC. We've left a placeholder at the two thirds interim analysis point.
 - Chen paper - Can only do sample size re-estimation before final analysis
 - Looks okay if we just have it once at 67%
 - They said simulations are okay if you have another interim look before that.
 - Theoretically, yes.
 - Would still go with 33% with efficacy and futility, and maybe 67% for SSR; and this would still fit in with Chen as long as we're doing it before final look.
- Futility
 - We did just mimic ACTT1 and ACTT2 and keep two interim points at 33 and 67%. 33% of 2000 ppl is about 700, so that's not very early, but people are randomized at 4 different arms. So, you have less than 200 in each arm. We don't know how fast recruitment will go.
 - I don't know how "liberal" – easy to kick someone out – we want to be with futility... if we want to make it fairly easy to drop a drug because we really need to see something that would really move the needle.
 - Right now, we've said conditional power less than 20% which is standard, but we can play with that.
 - We can do extensive simulations.
 - Philosophically, do we want to be "liberal" – if drug isn't looking like it's moving the needle, to stop?
 - Rate ratio of Remdesivir to placebo is about 1.31.
- Do we plan to pressure test what we're seeing at interim analysis with other master protocols?
 - In the RECOVERY protocol, they talk about their DSMC.
 - In RECOVERY, DSMC called the shots.
 - Not sure if we're in a world where DSMCs talk to each other and share results
 - The first study we're doing is meant to be quick. We should be nimble in our interim decision-making while holding on to statistical rigor.
- If we're powering for 1.25 hazard ratio, don't really see us increasing the sample size, but there's no penalty.
 - Would agree – we use sample size re-estimation more as an insurance policy. We start with a more optimized scenario saying we want 1.31 or 1.35. If we're not getting that by interim analysis, and we see that 1.25 is still clinically meaningful, that's when we increase the

Tuesday, May 5th, 2020

sample size. Otherwise, it's just a waste of subjects if you're doing 1.25 and say that if we get 1.15, we're going to increase the sample size. Doesn't make sense clinically

- If we're going to use 1.25, we should just stick with that, and if drug doesn't make it, they don't make it.
- Several papers that say if you're going to do this, it's more powerful and better to start with a larger sample size and stop early than it is to start with smaller sample size and try to increase
- Don't mind if we go from 1.30. It's reasonable to power it for this. But don't like idea of powering for much bigger rate ratio and then increasing sample size if we need to because it's more efficient to it the other way around.
- Question of how to be more efficient in saving the sample size. Okay as long as we don't go too big with sample size too early.
 - Think reasonable to use a power based on 1.30.
- Statistically, all of the compounds we're talking about have very low probability of success to come to whatever threshold we're discussing. That's more important to figure out how to kill the compounds then to talk about 1.25 or 1.30. We're spending a lot of time talking about success. We need to think about what will kill compounds early if turns out that they're not doing anything.
 - Not sure we should start at conditional power 20%
 - These are just low probability compounds
- Sub chair – if we go down from 1.25 to 1.3 (Elliott Levy strongly in favor of 1.25), and we go up to 73% recovery rate because of (b) (4), then we're down go 1400 total patients.
 - If you think there's any chance you'll need to increase sample size, better just to power for 1.25 and start with bigger sample size and start early
 - It buys you 600 people
 - If we all agree on a liberal futility rule, then we need to come up with it.
 - Would be based on a z stat or something
 - We don't need same futility rule for each drug because each will be compared against SoC
- Not likely that any of these drugs will have a clinically meaningful effect (prior probability low); concern that if study is too small, we'll complete it, create demand in marketplace, but we won't be able to do confirmatory study because no one will agree to be randomized to something else.
 - These drugs could be harmful as well as helpful, particularly immunomodulators; may have deleterious effect and make patients worse
 - May not be apparent from reviewing incoming safety data
 - There are a number of studies we're aware of that either have a 2-phase design where they screen and then confirm; or they're just screening protocols looking at smaller numbers of patients
 - That's our plan for the de novo.

Tuesday, May 5th, 2020

- If we start powering for 1.25 and have more aggressive futility rule – think that’s fine. If we start with 1.30 think that’s fine as well. We could just do for 1.25, have aggressive futility stopping rule, and we’re all set; no need for SSR if we did it that way.
- Sub chair
 - In the past, have played around with futility rules based on effect size
 - Have found that people are comfortable in the 15% range but once get over 20% chance of leaving something, people get nervous
 - Peoples’ comfort zones with this? If a drug truly does have an effect of 1.25, 20% of the time we miss it. Is that okay? Or are we more comfortable with 10-15% of the time we stop studying?
 - No objections to this.
 - Not sure agree. Need to understand the false positive in the false negative rate.
 - Simulation will be very comprehensive – will have a false positive rate, probability of false stopping, probability of leaving something on the table. The only thing that we need to be on same page about – is if we think we need a bigger sample size. Don’t want to get into situation where it’ll be a statistically significant trial, but the treatment effect will be small and won’t be very clinically meaningful. It can be bigger sample size, show stat significant, but have clinically moderate impact. If we’re okay with that and okay with simulation, we can answer all of these questions.
 - The more aggressive we are in not letting things through, the less likely we’ll let in something bad.
 - Highly likely that patients will need regimen rather than single agent to have benefit.
- Wonder how much efficacy left on the table on top of (b) (4)
- Likely that these drugs don’t have additive toxicities. Toxicities, to the extent that they exist, are likely to be orthogonal to each other.
- The smaller the effect size on time to resolution, the more important hard clinical endpoints on other end of scale are; and we’re not powering for those. It kind of depends on how well powered we are to exclude patients progressing to ventilation and death.
 - Sub Chair:
 - We can say what power we think we’ll have for the other endpoints if we fix the sample size to 1.25. We’re agreeing that we’ll go for a sample size that lets us detect 1.25. We’ll do early aggressive futility looks. TBD frequency and rule and will probably drop sample size re-estimation.
 - We’ll start with goal of just under 2000, with 73% recovery rate for the 3 drugs that we have.
 - Question remaining about how much efficacy left is good, as well as question on additive toxicities

Tuesday, May 5th, 2020

- On blinding and placebo
 - Aware of risk that we're running on the placebo. Impression is that the regulators are increasingly wanting to be confident that study integrity is there and are asking for robust blinding and placebo. In earlier discussions, it seemed like being pragmatic was top priority.
 - We can blind an injection with saline whereby a pharmacist is unblinded, but clinician isn't.
 - Subcutaneous product can be given IV as well.
 - We could have some sort of sham if you want.
 - You could also inject saline subcutaneous.
- For I-SPY protocol, FDA supports SoC only approach. So, the issue of placebos for drugs in initial feedback hasn't been raised by FDA.
 - This is a changing field.
 - Would love to blind but don't think realistic for many agents
 - I-SPY is designed to be like the *de novo* – with 2 stages – screening and confirmation stage
 - Haven't submitted their final IND packet
- Two of these drugs are IV. The third is an oral product and is in trials now. There would almost certainly be blinded placebo available.
- How easy is it to actually do this trial? Keeping it as simple as possible may be good.
- Is it possible to blind – FDA in general does prefer blinding. It's more interpretable type of trial, but the FDA is also cognizant of feasibility and logistic issues. If it's not a possibility to blind, the FDA has some flexibility but strongly suggest blinding when possible.
 - John Farley comment – part of the recovery definition that's subjective is "still needs medical care"
 - Maybe we could define clearly to make it less suggestive
 - Everyone could receive saline infusion and dummy pill on top of the (b) (4)
 - If oral placebo is available, the IV is easy, and you could have an unblinded pharmacist / put something in an opaque covering
- Other issue – endpoint that you're using – "is the patient ready to leave the hospital." This needs to be defined more carefully
 - Are drugs given for same duration? May effect time to discharge. Need more checking on this.
 - In the RECOVERY trial, took the time dimension out, acknowledging that duration of treatments are different
- Recap and next steps

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group
Ad Hoc Working Group Meeting, Key Takeaways

Tuesday, May 5th, 2020

- Get smaller group (Lisa, Sandeep, Mike, Sarah, and Eric) – put together appropriate pieces of protocol
- Sandeep – simulations
- Need to contact drug companies
 - Issue of putting drug on top of (b) (4) (DDIs): we don't have that data – when we outreach to companies, they may be able to provide information.
 - If request IBs and pharmacy manuals for all 3 of these compounds, should give us everything we need
- Need to clarify ordinal numeric endpoints

Chatbox

From (b) (6) to Everyone: 02:07 PM

Im confused as to whether we are talking about having a background of full anticoagulation?

From Lisa LaVange to Everyone: 02:07 PM

I think so — need to pick one.

From walter koroshetz to Everyone: 02:08 PM

not sure there is evidence for that at this time due to increased bleed risk with full dose. some hospitals might accelerate to that quickly

From Lisa LaVange to Everyone: 02:09 PM

Can we require all patients to be on some sort of anti-coat as background?

From Peter Wung to Everyone: 02:10 PM

Even with the allowance of background prophylaxis anticoagulation, we should definitely consider a stratification based on its use even though they may not be of "therapeutic" dose.

From (b) (6) to Everyone: 02:12 PM

Agree with Peter

I meant in analysis

From menons09 to Everyone: 02:12 PM

Agree too many stratification factors...

From (b) (6) to Everyone: 02:15 PM

Pretty sure that British guidelines recommend following D-dimer for guidance

ACTIV, Therapeutics-Clinical Master Protocol Sub-Group
Ad Hoc Working Group Meeting, Key Takeaways

Tuesday, May 5th, 2020

as to anti-coagulation

From PRICED to Everyone: 02:18 PM

Curious, will it be possible to blind given the selected immunomodulators?

From menons09 to Everyone: 02:19 PM

do we want to do blinded SSR ?

From PRICED to Everyone: 02:20 PM

Exactly, thanks Lisa.

From menons09 to Everyone: 02:21 PM

Not sure the rationale for Blinded SSR ?

From menons09 to Everyone: 02:42 PM

Agreed that we should do simulations with probability of false negative ...

From FARLEYJ to Everyone: 02:52 PM

Keith - could you remind us what the endpoint is for I-Spy?

From Keith Gottesdiener to Everyone: 02:59 PM

It is still evolving but likely to be time to recovery similar to ACTT1. But there are nuances, and the study is being designed to be very hard at allowing drugs to move on to some sort of confirmation part - really looking early on for "miracle" cures and ready to be harsh at stopping drugs that don't make that cutoff. Of course, all this is still not yet finalized, nor can I speak formally for the group, even though I'm fairly involved.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 12, Key Takeaways

Monday, May 4th, 2020

Action Items

Action Items		
	Information	POC
1	Send excel inventory of clinical trials	Stacey Adam
2	Circulate the initial triage and final scoring excel spreadsheets once reviewed by the Agent Prioritization Subgroup	Stacey Adam
3	Ensure updates on NHLBI/NINDS protocol moving forward	NHLBI counterparts
4	Set up ad hoc Master Protocol Subgroup meeting tomorrow	Stacey Adam

Key Takeaways

- Given results of Agent Prioritization process for first wave - we are currently looking at 6 drugs with 1 pending; definitely 5-6 drug candidates. For this wave of agent prioritization for the “repurposed” master protocol, no antivirals moving forward.
- Moving forward, the Master Protocol Subgroup needs to determine how to best study these 5-6 drugs that could actually go into a large confirmatory trial.
- Patient populations are getting treated with some sort of anticoagulant. Key question is how to approach dosing.
- Master Protocol Subgroup still needs to decide between the two options – to have one single protocol in factorial design or two separate master protocols for the repurposed.

Agent Prioritization recap

Recap from Co-Chair, Eric Hughes:

- Prioritization process worked well. We first did a triage and then numeric evaluation with the details of each compound later.
- It’s difficult to predict how a lot of the antivirals will act in the clinic because things that look at a single assay are not always predictive clinical benefit.
 - After much discussion, none of the antivirals rose to level of comfort with the WG.
- In terms of the immunomodulators, some of the compounds were very good; some had studies ongoing.
- Some that rose to the top were (b) (4) (not a lot of studies out there just yet; can be used in hospital settings)
 - Decision on (b) (4) is pending
- Symptomatic and supportive therapies – we all agreed that there is a need to understand how to treat thrombotic events that we’re seeing in many patient populations for COVID-19.

Monday, May 4th, 2020

- Low-molecular weight (b) (4) would be helpful to understand in this therapeutic area.
- Low-molecular weight (b) (4) would be at therapeutic doses instead of SoC, which we assume would be prophylactic doses of either low-molecular weight (b) (4).
- For the (b) (4) combination, the (b) (4) should be at prophylactic dose.
- (b) (4) discussion
 - This was triaged off because already in well-powered studies.
 - (b) (4) is already being evaluated in the extremely large (b) (4).
- (b) (4) – all triaged out because well covered by other well designed RCTs.
- We are trying to take into account that some studies were conducted in China and weren't accrued fully.
 - It's a difficult part of this process of not wanting to be duplicative but also not knowing what will be the fate of the trials that are ongoing. In some cases, it's clear that there are many trials happening; in other cases, there are a few medium sized trials.
 - Reminder to the group that this is NOT a singular process. Our main goal was to find the agents for the trial that this group is designing – agents ready for larger confirmatory study, to not compete with what was in ACTT2, etc. There are definitely compounds that were decently rated that will come back in the next round.
 - This was an extraordinarily difficult process with incomplete data and deciding by consensus is always challenging.
 - Were agents related to the angiotensin-Tie2 pathway considered, or are they more in the pre-clinical space?
 - These were not considered.
 - They may be appropriate for our next wave.
 - They may still be in pre-clinical testing and not in-patient testing. If they are not in patients, they wouldn't have been on this first wave list.
 - (b) (4) had a molecule in the clinic 10 years ago; (b) (4) has one; but none are approved.
 - **To recap, we are currently looking at 6 drugs with 1 pending; definitely 5-6 drugs candidates.**
- **Now, we need to figure out how to best study these 5-6 drugs that could actually go into a large confirmatory trial.**
- We will do more triaging for the de novo protocol.
- Suggestions from Agent Prioritization Sub Group – to options:

Monday, May 4th, 2020

- **Option 1:** Try to tackle 5-6 drugs in a **single protocol, in a factorial design** – keeping time to recovery as the primary endpoint; secondary endpoints would need to include decreased thrombotic episodes; and ensuring that networks have the appropriate expertise to handle both classes of agents
- **Option 2:** split these into **2 different master protocols**. This may be best option for timeliness.
 - Can split the 2 agent categories. Have the anticoagulant category go into the master protocol currently being drafted by NHLBI/NINDS and have the immune modulator category going into ACTT3. This would allow us to launch them faster in the end.
 - We want to make sure we have standardized primary endpoints, secondary endpoints appropriate to each, and to place protocols into appropriate networks suited for the agents. This may make things easier for the Clinical Trials Capacity Working Group.
- Factorial design – the concept is that we had two distinct sets of assets, and they address very different aspects of the pathophysiologic process. The sites are going to want to treat patients with agents from both classes, want patients to receive both immunomodulatory therapy and some antiplatelet /anticoagulant therapy. At the highest level, we need to decide whether there's a way for us to accommodate that in the study.
 - If we only looked at immunomodulatory for example, we may need to offer anticoagulants according to site SoC and lose the opportunity to evaluate in randomized fashion the benefits of different therapeutic approaches. It might be possible to address both these domains of therapy within single protocol rather than having to split into two.
 - In a 2x2 factorial, you'll compare drug A to control/placebo, but that will be averaged over the 2 levels of drug B; whereas what we'd been talking about instead was to compare everything to a pure control group. So, each arm gets compared to the same control.
 - Think this would be a 2x4 factorial design: have 3 different immune modulators if we want to test them all, plus a comparison group and 2 different approaches to anticoagulation. There wouldn't be equipoise for not having any anticoagulation in the hospitalized patient population.
 - In the analysis, are you comparing everything to the same control (which would not be a typical factorial analysis) or are we, for example, looking at, let's say, (b) (4) over control averaged across all conditions?
 - Think it's the average effect of (b) (4) analyzed across the different anticoagulation regimens.
 - This is how another WG member also interpreted, as with the first wave of (b) (4)
- **Option 1 or Option 2?**
 - WG member: Preference for first option - if we already set up in a factorial design, we may have to combine cocktails and can test later on down the road.

Monday, May 4th, 2020

- WG member: Problem with factorial trial – there may be interaction effect, so if you see interaction effects, it will be huge number of potential comparisons. You could have a negative interaction where the effect of something is good, but if you combine with other things, it diminishes the effect. Things get complicated if you intend to start looking at what happens when we combine x drug with y drug. You're getting a huge number of comparisons, and that generally calls for multiple comparison adjustments.
- Is it possible to have 3 immune modulators and 1 anticoagulant; and have everything be given with 1 anticoagulant, so we're just testing which is the better immunomodulator?
- What we're hearing from the blood community: everyone's getting some form of anticoagulant. There are questions about how best to do it, but there isn't a question about whether something should be done in hospitalized population. So, if we don't address anticoagulant in protocol, it will be up to the SoC, so up to sites. We might want to record that. There will be variability. If we want to control it, we'd need to randomize.
 - Sub Chair: We should control with one anticoagulant.
- It will be tricky to control it. Particularly as the disease progresses, they're not going to stick with one. They're going to accelerate the potency. We're hoping that immune modulators will suppress the clotting problem, which is one of the potential triggers (in addition to the virus itself). The immune response to the virus can also trigger the clotting system. The issue is that if you don't control it, these interactions will be out there but you won't be able to figure them out. If you do single master protocol, you have a chance of seeing when they pop up. The danger would be if there's a negative interaction between the two of them. Then you're sunk.
- We want to ideally test 3 diff anticoagulation strategies. How can that be layered on top of 2-3 immunotherapeutic? Assuming the SoC is (b) (4)

- SOC is more complicated than that. People who are hospitalized and not severely ill and with relatively low (b) (4), but as D-dimer levels go up and becomes more complicated, anticoagulation accelerated more towards full-dose heparin; sometimes people are doing beyond that because of the level of coagulation they're seeing.
 - Is this more reason to have a separate protocol?
 - Complicated issue regardless of whether in single protocol or two protocols
 - Not sure about right answer.
- NHLBI and NINDs have been thinking about trials that would be deep, rich, more complicated trials in this space. We can try to get nuances of what's the algorithm for accelerating treatment of thrombosis in COVID-19 patients. This may not be simple trial. This will be really important.

Monday, May 4th, 2020

- Issue for ACTIV MP sub group – whether to put order to the chaos or to try to prospectively set things up so you can try to understand the interactions and best treatments from the variability observed.

NHLBI/NINDS master protocol idea

- NHLBI and NINDS, with probable buy-in from (b) (4) and other entities, working on a large platform for anticoagulation – a “platform of platforms” or “network of networks.”
- Some basic components on which we’re building are from trans-agency collaboration for trauma-induced coagulopathy, which also includes radiation.
- This has been very instrumental in helping us understand endothelial injury in this context. The more that comes out about COVID-19, the more it’s clear that endothelial injury is a hallmark of this disease. Studying the pathogenesis of this is critical.
- We have infrastructure on which to build the ability to do this in the context of meticulous clinical trials across the full spectrum of COVID – from the moment of ascertainment with a COVID-19 test to progression towards in hospital care, subdivided between that requiring hospitalization alone vs. that requiring cardiopulmonary support.
- Part that hasn’t been looked at – convalescent period.
- We’re developing protocols for this and large amount of expert networks to do this. We’re well along in assembling groups of networks.
 - Include NHLBI networks – SIREN, PETAL, cardiothoracic surgery network; some of NINDS networks, acute injury research, stroke network. We’re trying to cover the relevant endothelial injury states across the board.
 - Artery, arterial, microvascular, up through venules and venous system where clots are happening in strange places and strange ways like coronary veins.
- We have expertise from some of the best people in the world, including people crossing over between classical clotting and cardiovascular disease.
- We’re looking at how to put pieces together.
- We have a lot of experience collecting meticulously very difficult specimens to obtain in sick patients – critical to understanding pathogenesis. Not every participant in network of networks will be expected to do this; but there will be people who have done this and can do it well.
- We’ll add in immunomodulators – added to anticoagulants and antiplatelets. Megakaryocytes are showing up in places outside bone marrow where they don’t usually shed platelets.
- We’re hoping to pull this off quickly. Proposal presented within NHLBI this week. If it goes well, we may be able to move this forward dramatically in the coming 1-2 weeks.
- Dr. Gibbons and Dr. Collins have had convo on how to best mold above thoughts with ACTIV going forward. Another conversation is to follow today.
- For this group, the question is whether or not to include some type of layered-on anticoagulant trial to regularize what the patients will be seeing when you add on your immunomodulatory therapy or antiviral.

Monday, May 4th, 2020

Remaining questions

- Sub Chair: Do we know how to standardize anticoagulant therapy?
 - If you have trial where people agree we'll randomize between the two, the trial would have to include a crossover. We think there's enough equipoise for this now.
 - Don't think there's equipoise in hospital
 - Can't randomize once they're in hospital
 - Thinking about therapeutic unfractionated vs. therapeutic low molecular weight as a first pass
- So, if we have 3 immune modulators of interest and 2 approaches to therapeutic anticoagulant treatment – that's still a complicated design.
- Sounds like in terms of anticoagulants, everyone is getting treated with something. Everyone needs therapeutic. Our SoC would have to be the single arm or two. But then the immunomodulator is laid on top. So, you'd have 6 combinations, and their comparison would always be to the anticoagulant without the immunomodulator. That would be 6 cells and no true SoC. True SoC is some type of anticoagulant therapy.
 - Too many missing cells? Not a factorial. Assumes a baseline for anticoagulants but question as to which one; and adding an immunomodulator to it, and there's 3 of those.
 - So, you have 6 vs. 2 SoC. You still could have interactions that don't make sense. The anticoagulant is there no matter what.
- Can we eliminate some at interim? In the technical sense, this is not a factorial design. We do a typical factorial design based on the doses now. Here, in principle, the analysis at least in the way it will be designed won't be factorial. WG member preference would be if we can, in WG discussions, talk about how many arms.
 - We end up comparing this to 1 or 2 SoC and have plan of weeding out one or multiple of these analyses at interim.
 - Start thinking from this premise and then build on
- Sub Chair: there's no cell that doesn't have therapeutic anticoagulant. The question is what the better way to approach dosing.
- Is therapeutic anticoagulation really SoC? Where does it say that?
 - There's no equipoise. It hasn't been proven. Guidelines are still prophylactic dose. Things are changing quickly.
 - It's been inferred that this is the right thing to do from fact that you're seeing so much microvascular injury. When you've damaged that much endothelium in capillary bed, then you're in trouble.
 - Anticoagulation – you're going to see something. No one's not going to get anything. In terms of number of cells, how much can you handle if you want to test the 3 immunomodulators. How many cells can you handle, and if you don't do it this way, when

Monday, May 4th, 2020

you randomize, then how will you deal with interactions that you could see due to random variable use of these different anticoagulants?

- One could use a baseline covariate as to what type of anticoagulation you're using, so there'd be different approaches to that. It would be tricky if things are changed later – not at baseline but after someone's already on treatment. This gets complicated because in response to perhaps poor outcomes, which becomes more difficult statistically.
- We've got (b) (4) across the board and 3 immunomodulators on top of (b) (4).
- Concept of weeding out early can serve you in factorial designs – do we have to use “time to recover” to weed out earlier?
 - Moving to potential care unit
 - Progression to intubation
 - Some other outcome that's predictive of a bad outcome/good outcome. Possible we could use something else for futility

Chatbox

From (b) (6) to Everyone: 01:06 PM

Eric: can you say a bit more about your discussions regarding (b) (4) ?

From RUBIND to Everyone: 01:08 PM

(b) (4) is also being evaluated in the extremely large (b) (4).

From Stacey Adam to Everyone: 01:08 PM

Thanks, Daniel

From David Goff to Everyone: 01:09 PM

What about (b) (4) ?

From Sandeep Menon to Everyone: 01:11 PM

Was (b) (4) considered ? Or was it excluded given (b) (4) is already on a trial ?

From walter koroshetz to Everyone: 01:11 PM

also a large number of the trials were from China and they may have ended due to lack of patients

From tenar001 to Everyone: 01:12 PM

We are automatizing a daily download of all COVID trials in CT.gov using our AACT database. Let me know if you would like access to that until we upload it to our website

From David Goff to Everyone: 01:14 PM

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 12, Key Takeaways

Monday, May 4th, 2020

Were agents related to the angiotensin-Tie2 pathway considered or are they more in the pre-clinical space?

From walter koroshetz to Everyone: 01:14 PM

My understanding is that there are standardized processes for comparing potency of anti-virals. Driven by (b) (4)

From Stacey Adam to Everyone: 01:15 PM

Thanks, Pam. I will keep you posted. (b) (4) is doing some thing similar for us with both clinicaltrials.gov and WHO. I will follow back.

Hi Walter, yes, we had (b) (4) give us a download on their testing. We will stay in touch with them.

From tenar001 to Everyone: 01:16 PM

is anyone comparing notes with the (b) (4) ?

From Stacey Adam to Everyone: 01:17 PM

Hi Pam, yes, we are working on discussions with (b) (4)

From Peter Wung to Everyone: 01:21 PM

Does the sponsor company ultimately have to approve the inclusion of their respective compounds into the study? If so, should we have back-ups ready in case the sponsor company does not agree to the use of the prioritization compounds for this study?

From Stacey Adam to Everyone: 01:23 PM

Hi Peter, yes, I do believe the sponsor needs to approve, although some are marketed agents which could just be purchased if we felt strongly, but this would not be the preference.

And yes, we may need to have back ups. We will be reaching out to the companies soon.

From Sandeep Menon to Everyone: 01:26 PM

Technically it is not a factorial design in the strict sense...

we may not be powered for a regular factorial design?

From (b) (6) to Everyone: 01:28 PM

I prefer the first option in part to better control SOC.

I am also concerned about testing too many agents in this first round

From Sandeep Menon to Everyone: 01:28 PM

We also do not know the magnitude of the interaction effects and it will get messy very soon..

From (b) (6) to Everyone: 01:29 PM

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 12, Key Takeaways

Monday, May 4th, 2020

too many agents

From Sandeep Menon to Everyone: 01:29 PM

we still do not know if it is synergistic or additive...

From Sandeep Menon to Everyone: 01:49 PM

We can weed out few of these combinations at interim ?

From (b) (6) to Everyone: 01:49 PM

how sure are we that therapeutic anti-coagulation is standard-of-care?

From Mike Vincent to Everyone: 02:00 PM

Sorry - have to drop off

From walter koroshetz to Everyone: 02:02 PM

for anticoagulation if drug doesn't drop the d-dimer then not working,

High-Level Meeting Summary

The Agent Prioritization Subgroup of the TX-Clinical Working Group (Sub-WG) learned from Dr. (b) (4), (b) (6) about potentially relevant lessons from a parallel effort called the (b) (4) (b) (6). Sub-WG members made minor adjustments to and clarifications of the scoring process, which they will complete this weekend.

A summary of key discussion points follows.

Lessons from the (b) (4)

Dr. (b) (4), (b) (6) described a parallel agent prioritization process conducted by the (b) (4) (b) (6). Although that effort has different selection criteria from ACTIV (it focuses on (b) (4), (b) (5) that can be delivered cost-effectively and at scale in low- and middle-income countries), it may nonetheless offer underlying data and lessons learned that are relevant for ACTIV. The (b) (4), (b) (5) is posting all of its screening results online, and Dr. (b) (4), (b) (6) will share with ACTIV the data underlying its decisions. Participants discussed several specific challenges.

Agent Identification

(b) (4), (b) (5) has utilized three primary sources to identify agents: the (b) (4), (b) (5) collection, a comprehensive library of registered drugs and drug candidates; pharmaceutical company nominations; and internal expertise (i.e., (b) (4) scientists).

Preclinical Data on Antivirals

Dr. (b) (4), (b) (6) cautioned that certain *in vitro* cell lines may be generating a high volume of false positives and negatives in currently available preclinical data. For example, (b) (4), (b) (5) on their surfaces, so compounds that work via that mechanism cannot be reliably tested in that line without modification. Dr. (b) (4), (b) (6) noted that the (b) (4), (b) (5) had to compensate for such challenges in data on the drugs they were considering (such as (b) (4), (b) (5)).

Immunomodulators

(b) (4), (b) (5) considers neutralizing monoclonal antibodies a high-priority drug class; it has already invested in manufacturing capacity to ensure low- and middle-income countries have access to these agents when they become available. The Sub-WG noted that (b) (4), (b) (5) discussed whether to remove it from the ACTIV list; Dr. (b) (4), (b) (6) responded that this agent is not currently being tested anywhere, so members decided against removal.

Supportive/Symptomatic Therapies

Anticoagulants are also of interest to (b) (4), (b) (5). Initially identified candidates that meet its logistical criteria (e.g., aspirin, heparin) have not generated promising data. (b) (4), (b) (5) and will not be identified until later in May.

Clinical Trials

Similarly to ACTIV, (b) (4), (b) (5) is working with established clinical trial networks, in its case through (b) (4). Dr. (b) (4), (b) (6) noted that (b) (4), (b) (5) does not wish to assume the function of a PI.

The Scoring Process

The Sub-WG members have received updated scoring forms that incorporate changes discussed in the group's April 30 meeting as well as the subsequent addition of new supportive/symptomatic therapeutic agents. Several members have submitted scores already, and the remainder will complete the scoring process by Sunday, May 3.

Adjusting the Scoring Spreadsheet

Drs. John Mellors and Keith Gottesdiener both noted that the current scoring spreadsheet does not allow reviewers to indicate that they have insufficient data to assess a particular criterion. Sub-WG members agreed to adjust the spreadsheet to allow such a response. When all scores have been tabulated and the list of agents narrowed, Sub-WG members will carefully review each scoring column to make final recommendations.

Looking Ahead to the Next Wave

In response to a question from Dr. Carl Garner, the group clarified that monoclonal antibodies will be considered by ACTIV. They were excluded from the first wave in favor of repurposed agents that were immediately available for trials; however, they will be addressed in the next prioritization cycle.

Next Steps

Dr. Stacey Adam will recirculate the adjusted scoring spreadsheet. Members will submit scores to her by 12pm ET on Sunday, May 3, in preparation for finalizing recommendations for the first wave by Sunday evening. At its first meeting next week, the Sub-WG will have its first opportunity to reflect on a complete prioritization cycle. Feedback from Sub-WG members will be applied to revise the process before the next prioritization wave begins.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke*

Elliott Levy, MD, SVP, *Global Development, Amgen*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomatics Capital; Therapeutic Accelerator Lead, Gates Foundation*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 11, Key Takeaways

Friday, May 1st, 2020

Action Items

Action Items		
	Information	POC
1	Share paper regarding endpoints (China trial, NIAID)	Lisa LaVange / Stacey Adam
2	ACTIV needs to begin conversations on getting (b) (4)	ACTIV Leadership
3	Develop plan in the case that ACTIV cannot get (b) (4)	Master Protocol Sub Group
4	Remaining discussion items include: - Futility and safety boundaries still need to be defined. - Time to mortality also needs further discussion.	Master Protocol Sub Group

Key Takeaways

- Aim is to try to pull (b) (4) into the protocol. Consensus is that we will have (b) (4) in background as SoC, and the other drugs on top: (b) (4) + antiviral, (b) (4) + immunomodulators, (b) (4) + anticoagulation.
- Concern from the group around uncertainty of ability to get (b) (4) ACTIV needs to develop a plan if we are not able to get (b) (4)
- Suggestion that we write (b) (4) as SoC, applied locally, where available, and if we can supply, then we can supply. If we can't, then it will be the best SoC in any location.
- Futility and safety boundaries still need to be defined. Possible to have different futility rules for each of the arms. Time to mortality also needs further discussion.

Changes to consider now that (b) (4) is SoC

- Group consensus: Would be ideal to have (b) (4) If we can get it, it would be great to pull into the protocol.
- When we know what the actual agents are, discuss if there's anything we want to add on to (b) (4)
- Concern from the group around uncertainty of ability to get (b) (4)
 - According to ACTIV leadership, (b) (4) has been agreed to for ACTT2, but there have been no understandings or agreements beyond that. ACTIV would need to begin those conversations now.
 - (b) (4) has decided to join the partnership.
 - Suggestion that we write (b) (4) as SoC, applied locally, where available, and if we can supply, then we can supply. If we can't, then it will be the best SoC in any location. We may need to refine this when we know the answer.
 - Group support for this suggestion.

Friday, May 1st, 2020

- Did we agree on whether 5 or 10-day course will be used?
- Suggestion to use an augmented control arm with some of the existing data from (b) (4) trials. Subgroup Chair sent a paper describing this to the co-chairs. It will be distributed to the group.
- Comments from Subgroup Chair on ACTT3:
 - We are trying to borrow as much as we can from ACTT2, but ACTT3 is very different from ACTT2. It's still a master protocol but won't be as controlled.
 - The drugs we're evaluating may not have anything to do with each other. We're trying to see if each with a SoC is effective.
 - We have a lot of data on (b) (4) from ACTT1; there are a lot of people, including investigators at UNC, strongly proposing to meta-analyze (b) (4)'s real effect on different endpoints. So, we should exercise flexibility as we would with any master protocol and bring in external controls and concurrent controls if it's not (b) (4).
 - Subgroup Chair suggests we worry more about early stopping, and if it's not early stopping, then something else that's predictive to early recovery.
 - We do have flexibility. We don't have to treat each of our drugs the same.
- Suggestion to stratify by (b) (4) individual patients.
 - May depend on what the indication is – could be non-ventilated, ventilated.
 - We could probably look at it by sites.
 - Need to keep in mind that there will be demand for (b) (4) in other parts of the world too. This could get political.
- Rationale and connection for (b) (4)
 - Mike Proschan: Uncertain.
 - Idea of stratifying – to compare in the sites with (b) (4); you'd have (b) (4) plus another drug vs. (b) (4); and in other sites, you'd have these drugs vs. SoC. If you assume that the effect of a given drug is the same whether it's on a background of (b) (4) or on a background of SoC, you could combine those results; but that's a big assumption. It could be the same.
 - Another WG member: not sure if it would be the same.
- Need for alternative plan if we can't get (b) (4)

Discussion on Combination

- Subgroup Chair: If we get another antiviral agent, are we adding it together with (b) (4) Combination may be great, but sometimes you just need another drug.
- Co-Chair: Key question – can you get more effect with two Mechanism of Actions (MoA)? Would want to do know what the combination does.

Friday, May 1st, 2020

- Subgroup Chair: Want to know what the combination does if we also know what the monotherapy does. We have 3 arms already with 3 different drugs, and we don't know if we'll have the luxury to test the combination in the monotherapy.
- WG members suggesting combination.
- Depends on the MoA of new agent. Is there a biologically plausible reason why combination should be better? A rational combination would make sense.
- Don't think combination antiviral therapy should be assumption. Combination antiviral therapy is probably not going to be as important as some sort of adjunct. If we go with an adjunct, seems really difficult to look at anticoagulation vs. (b) (4) and anticoagulation vs SoC without some kind of antiviral.
 - Another WG member: With HIV, we did learn that sometimes using two drugs did have an additive effect. The HIV experience didn't suggest that you needed orthogonal mechanisms in all cases to get the effect. Resistance plays major role in current regimens, but in early days, sometimes it was important to get two to beat down the virus enough. Don't think any of the other molecules are duplicates of (b) (4).
- Convalescent plasma – can this be something we use with (b) (4) in this trial?
 - There are efforts to do convalescent plasma trial within SIREN network. There's interest in getting (b) (4) but not sure if they'll be possible to do that. This will be in non-hospitalized patients. Idea is to give a dose of the plasma in ER to people who are not ill enough to require hospitalization.
 - Same plan with hyper-immune trial
 - Convalescent plasma was triaged off for ACTIV.
- How will indications for hospitalization change over time?
 - Interpretations currently suggestions earlier better than later. Now that we have (b) (4) and people believe it's better if given early, the threshold may go down.
- Need to look at different combinations of MoAs and test against (b) (4) and see how it will play out. Maybe worthwhile to consider having (b) (4) in background. (b) (4) + antiviral, (b) (4) + immunomodulators, (b) (4) + anticoagulation. We'll need to look at effect size and how will affect the study.
 - But need to see how those combinations of MoAs will alter the disease
 - Subgroup Chair: this is the plan for now. Is to have the SoC and the new drugs on top of that unless there is a safety issue or something that will keep us from doing combination.

Discussion on idea of confirmatory trial, futility boundaries

- Question of whether we really will have 3 drugs, given Peter Steins' comment in previous Agent Prioritization Subgroup Meeting –
 - Clarification from Stacey Adam that Peter Stein was trying to emphasize that whatever the Agent Prioritization team brings forward is truly intended for a confirmatory trial. Otherwise, we need to pivot and rethink our idea of a confirmatory trial. He wasn't very

Friday, May 1st, 2020

excited about final candidates on list because there are other things in the works that are not in public awareness right now. He just wants us to do our due diligence.

- WG member: Peter attacked the strategy of the trial. You're testing drugs that may not work. Is that a good idea? Has anything really changed despite what Peter said?
- WG member: Can we adjust for futility for agents that aren't as far along?
 - Subgroup Chair: We have to decide on time points for futility. The plan is to figure out the futility boundaries once we know what the agents are and same thing for the safety boundaries.
 - WG member support for more rapid and stringent futility analyses. Our strategic answer to Peter should be – we're starting with a lot of people, but we expect that many of these drugs will declare themselves early on. And that would solve the problem of wasting a lot of patients if there's nothing there.
- Futility boundary discussion continued:
 - Should we let futility boundaries vary by drug? Having a futility stop for another antiviral may be different from an anticoagulation.
 - WG member: Not sure if companies would buy into this.
 - WG member: Is our philosophy to rapidly decide to kick things out of this trial or to really make sure that if any of these agents have a small effect, we are sure to capture it? This depends on what we think about the molecules. What do we want to get out of this protocol?
 - Suggestion that we're looking at low probability compounds, and we should clear them away pretty quickly.
 - Subgroup Chair: philosophy is to be liberal with early stopping
 - WG member: supportive of idea to power for detecting moderate effect and stopping early if there's nothing there.
 - Clarification from Subgroup Chair:
 - Can we apply futility rule differently to each of the arms?
 - Subgroup Chair: We are treating ACTT3 somewhat like a master protocol. We're trying to share control arms between 2-3 studies if we have; but it's not exactly a 4-arm trial. Believe we will have different safety boundaries. If we have really different classes of drugs, then safety stopping rule doesn't have to be different but might be different. Could be different futility rule because adjunct therapy may not sway anyone's opinion on how to treat people if it doesn't really do something on top of (b) (4) it's possible. Not sure if it's wise but is possible.
 - WG member: example – anticoagulation could have tremendous bleeding risk. So might need different safety monitoring. The reason for giving anticoagulation has to do with vasculopathy and coagulopathy that doesn't happen to everyone, but

Friday, May 1st, 2020

- when it happens, it can be devastating. Taking same approach to this as we are to antivirals may not be best idea.
- WG member: think we'll need the futility rules based on what we know of the landscape. The futility rules can be different.
- Subgroup Chair: We should talk about time to mortality, too.
- John Farley: mortality p-value was .059
- To detect 1.25, it takes about 1,000 for just 1 drug vs. SoC; 1500-1600 for 2 drugs; and about 2000 for 3 drugs that we're going to get.
 - The sample size will move down if you want to go back to the 1.35, but members of the group did not want to do that.
 - We can also try to get early stopping, but that won't help us get our supply of (b) (4)
 - We'd have to do a simulation computing a sample size depending on futility and early stopping rule; but if we really want to move off of this number, we need to change our RRR or endpoint.
- Blinded recovery rate (ACTT)?
 - Mike Proshan – it's very close to what we thought it would be. Around 70%. It's a little bit higher but right around 70%.

Endpoint

- If we do prioritize an anticoagulant, does this endpoint still make sense?
- WG member: Happy with endpoint that we chose because easy to explain. Time to recovery is very easy to explain to everyone. There may be things that could be more powerful; it's not dramatically different power, depending on the assumptions you make. This endpoint has a lot of advantages.
- Lisa to share paper – simulations re: endpoints. They just updated paper with China trial in NIAID results.
- WG member: do think that endpoints (not virologic) would still apply.

Recap and Next Steps

- Update from Stacey Adam: We just learned from Clinical Trial Capacity Working Group that there are other Master Protocols that are being written and being launched. We didn't know they were so far along. Related to anticoagulation in PETAL network in NHLBI/NINDS. We want them to come and present to us. There's also a master protocol for in hospitalized patients at the VA.
- We're working to get them to come and talk to us.
- Next week, we have REMAP-COVID on Friday – the Study PI and their statistical team.
- We have a query out to I-SPY-COVID.
- Update to team – Agent Prioritization will try to wrap up prioritizing first wave of agents by Sunday evening. The soonest that we'll have the agents is Monday, 5/4.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 11, Key Takeaways

Friday, May 1st, 2020

Chatbox

Sandeep Menon 11:30

Mike/Lisa — if we do not get it, any appetite with regulatory to use (b) (4), (b) (5) approach using it as augmented control ?

Sandeep Menon 12:23

We can have a lean arm with (b) (4) in that case ? would be still tricky if we want to understand a combo effect...

Sam Bozzette 14:36

the optics of a trial with a non (b) (4) control will be tough - though I get the rationale the knee-jerk reaction will go to whether it is an ethical study

Sandeep Menon 15:19

agreed. But we will need to come up with some options if we do not get (b) (4) in our trial.

markde 15:31

Even when / if the EUA is approved, (b) (4) has only 140k treatment courses currently (unless 5-day regimen can increase this). It's not enough for all RCTs to use as SOC.

Sam Bozzette 15:49

sometimes reality is most inconvenient

Sandeep Menon 16:08

Concur.. 😊 😊

markde 16:16

Yes. True.

Sandeep Menon 18:20

Eric/Keith/Sarah — do we need to consider DDI if we add (b) (4) Something ?

Markde 19:57

Is there a way to get access to ACTT data? We are flying pretty blind right now.

Peter Wung 31:42

Is it possible to have 4 arms being: (b) (4) +AntiViral vs. (b) (4) +Immuno vs. (b) (4) +Anticoag to account for the different combinations with regards to MoA?

Eric Hughes 36:45

I like that thought

High-Level Meeting Summary

The Agent Prioritization Subgroup of the TX-Clinical Working Group (Sub-WG) discussed progress on prioritization scoring. The Sub-WG agreed to seek additional data on antiviral agents that passed triage tests and to assess whether the level of available data warrants adjustments to plans for ACTT3 and the first wave of clinical trials.

A summary of key discussion points follows.

Additional Agents for Scoring

Participants addressed the omission of several agents of potential interest from the ACTIV Compound Inventory ('the Inventory') and considered its implications for the broader triage process.

Dr. Keith Gottesdiener noted during the previous Sub-WG meeting that several immunomodulators identified by the R&D consortium and submitted to the Inventory did not emerge from triage. Dr. Stacey Adam investigated and found that these agents had been inadvertently omitted from the triage process. The Sub-WG agreed to correct this oversight by inviting Drs. Gottesdiener and Elliott Levy to review 11 mistakenly omitted agents against the triage criteria; the Sub-WG anticipates that this review will add between 5 agents to the scoring process, which will otherwise continue unchanged. The potential additional burden on immunomodulator reviewers will be offset by movement of three agents (b) (4), (b) (5) from the immunomodulator to the antiviral agent class.

Several participants noted that other agents were also excluded at the triage stage that may hold more promise than the agents being scored, and thus asked whether the triage process should be more broadly reopened. The Sub-WG decided against this course; however, they distinguished between correcting an error in the agents submitted to triage and revisiting the triage criteria themselves. They noted that the Sub-WG is implementing a methodical process that allows appropriate adjustments to triage criteria during subsequent prioritization waves.

The Impact of Inconsistent Data on Agent Classes

Participants noted that the quality of preclinical data on antiviral agents may complicate scoring. The demonstrated performance of an antiviral agent in the controlled conditions of cell culture is critical to determining whether it has any chance of working in humans. However, in many cases available preclinical data lack scientific rigor (e.g., they may stem from just one report; or when multiple reports are available, they may use vastly different micromolar levels or assays, making them hard to compare).

Dr. Joseph Menetski suggested that data weaknesses could themselves be considered a data point during the prioritization process (i.e., any agent with weak or inconsistent data would be deprioritized and considered in subsequent scoring rounds). However, Dr. Peter Stein argued that this approach will cause an undesirable de facto elimination of antivirals from the first wave. Antivirals, he noted, may currently represent a more promising class of agents than

immunomodulators, which target pathways that are not yet understood in the context of COVID-19.

Fill Gaps in the Data

Participants discussed ways to address inconsistent preclinical data. They agreed to solicit and review additional data from a range of sources, including the TX-Preclinical WG, NIH's ongoing intramural and extramural data collection, ACTIV's representative from the Gates Foundation, and a screening effort underway at Dr. Draghia-Akli's institution, KU Leuven. (While all of these sources are intended to address gaps in antiviral data, Drs. Gottesdiener and Levy will also provide one-page overviews of the additional immunomodulator agents they are identifying.) Any data obtained from these sources will be considered during the scoring process.

Adjust Clinical Trial Recommendations if Necessary

Participants recognized that their efforts may not overcome the data weaknesses they have identified. Once the scoring process is complete, the Sub-WG members will consider whether the data available for the top-scoring agents warrants alterations to the clinical trial process. If agents do not satisfy the Sub-WG members' "expert gestalt" assessment, they may recommend either (1) running adaptive Phase II trials instead of moving directly to large confirmatory studies in ACTT3 or (2) taking more time to collect all data necessary to make Phase III trial recommendations.

Next Steps

Dr. Adam will update the list of agents based on today's discussion and will circulate the revised list along with all additional data she is able to collect related to candidate agents. The Sub-WG members will complete the scoring process in preparation for formulating recommendations. As this work advances, the Sub-WG will also record observations and suggestions for improving the prioritization process to help refine it during subsequent waves.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

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STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group
Working Group Meeting 6, Key Takeaways

Friday, May 1st, 2020

Action Items

Action Items		
	Information	POC
1	(b) (4), (b) (6) to share documentation on (b) (4), (b) (5)	(b) (4), (b) (6)
2	Update scoring sheet with option in columns for “don’t know”	Stacey Adam
3	Complete scoring of agents, and reconvene on Sunday, May 3 rd	WG Members

Key Takeaways

- (b) (4), (b) (6) overview of (b) (4), (b) (5) consideration working principles, (b) (4), (b) (5)
 - (b) (4), (b) (5)
 -
 - Will post all screening results to publicly available website.
 - Actively looking at manufacturers for everything that could be in play. They’re looking at model cases of simple molecule uncomplicated manufacturer – what do you need to do to tie up a contract manufacturer; or at the other extreme, parental extreme difficult synthesis - what does it take? They're trying to be ready for when they find something.
 - The (b) (4), (b) (5) is already working with established networks and is acting like a sponsor. The (b) (4), (b) (5) has very good operational experts inside of it but don’t want to take over the function of a PI and instead want to support the PI.
 - (b) (4), (b) (5)
 - (b) (4), (b) (5)
- Scoring
 - On scoring sheet, would be helpful to have an option in the column heading to indicate “don’t know/can’t find answer”
 - Suggestion to go through some compounds column by column and align

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) Co-Chairs updated participants on the progress made by both the Agent Prioritization (AP) and Master Protocol (MP) Subgroups. Participants reviewed the current shortlist of triaged agents being considered for repurposing and discussed how the agents triaged so far, as well as the expected Food and Drug Administration (FDA) approval of (b) (4) this week, may affect the Drug Repurposing MP design (i.e., ACTT3). The WG also confirmed next steps, timelines, and future WG and subgroup meeting schedules.

Agent Prioritization Subgroup Update

The AP Subgroup screened an initial list of approximately 400 agents for clinical readiness to establish a list of approximately 170 agents for further triaging by mechanism of action (MOA) and need for further evaluation (i.e., are existing trials already studying agents or MOAs with sufficient rigor?). The AP Subgroup has completed this triage and retained approximately 20 agents for detailed assessment and prioritization by an Expert Panel using the AP Criteria and Scoring System. The Scoring System will be used to help guide the Expert Panel's discussions but will not by itself decide agent prioritizations. The AP Subgroup aims to select three to five agents for entry into ACTT3 by Sunday, May 3. Participants clarified that although agents are being assessed in three primary categories (antivirals, host-targeted/immunomodulators, and symptomatic/supportive therapies), prioritization aims to select the three to five best agents regardless of class. Although some participants suggested potentially including immunogenicity in reviewing any biologics, others emphasized that ACTT3 studies will be too short to raise immunogenicity concerns (later prioritization waves that include monoclonal antibodies may, however, assess immunogenicity). The AP Subgroup has been including a science writer in all of its meetings to ensure documentation of its discussions and prioritization decisions; these records are accessible for MP Subgroup members to review.

Anticoagulants

All symptomatic/supportive therapies included in the triaged shortlist are anticoagulants. The MP Subgroup has not yet determined whether these compounds will be tested under the same MP as the antiviral and host-targeted therapies (which could become complicated), or whether anticoagulants could be tested separately. Many COVID-19 inpatients receive an anticoagulant already, and systematizing doses for a target patient group across several hospital sites could enable effective study of a selected anticoagulant without integrating it into the ACTT3 MP. However, this decision will ultimately be informed by the final set of agents selected and the resulting MP design, and it may require discussion with the ACTIV Leadership Group.

Dr. Walter Koroshetz expressed cautious optimism that the usual excessive bleeding caused by anticoagulants have not generally appeared in COVID-19 patients. Dr. Judith Currier also noted (and several participants agreed) that given FDA's expected approval of (b) (4), a combination trial of (b) (4) and a selected anticoagulant may be fruitful.

Master Protocol Subgroup Update

The MP Subgroup has focused on designing “ACTT3” (i.e., its amendment to the National Institute of Allergy and Infectious Disease [NIAID]’s ACTT2 protocol) to assess the AP Subgroup’s top prioritized agents for potential repurposing. FDA’s approval of Remdesivir will affect sample size and standard of care (SOC) considerations for the design of ACTT3.

Reviewing the MP Subgroup’s current plans for ACTT3, Dr. Peter Stein of FDA noted that the design resembles that of a large confirmatory trial rather than of a small screening trial, but that the compounds included in the AP Subgroup’s shortlist of agents lack robust preclinical or early clinical data in COVID-19 models or patients (i.e., suggesting a low probability of success). He questioned the effectiveness of conducting large trials to test agents with little evidence of efficacy in treating COVID-19. Dr. Keith Gottesdiener agreed with Dr. Stein’s analysis.

Dr. Lisa LaVange confirmed that the ACTT3 protocol aims to rapidly assess FDA-approved agents with known safety profiles for *potential* efficacy in treating COVID-19 inpatients. In contrast, the more comprehensive *De Novo* MP will aim to generate robust Phase II data on a broader range of candidate agents before testing them in confirmatory Phase III trials.

Dr. Stein also pointed out a potential logistical challenge to ACTT3 trials: rates of new COVID-19 cases are now slowing, which could hinder efforts to rapidly recruit the number of patients needed to execute the ACTT3 study in the envisioned timeframe.

Dr. Sarah Read emphasized that decisions about these challenges cannot be finalized until the final prioritized list of agents becomes available on Monday, May 4. The MP Subgroup may, for example, decide to expand the number of test sites or adjust the recovery rate ratio.

Dr. Elliott Levy recommended that ACTT3 search for modest effects that may still meaningfully benefit patients and providers, and Dr. LaVange suggested addressing Dr. Stein’s concerns by fine-tuning the ACTT3 futility analysis to require early and frequent monitoring of intermediate endpoints, and to require relatively high success thresholds to continue recruitment/testing. Dr. Stein endorsed this approach, and the MP Subgroup will meet tomorrow to discuss these issues in more detail.

Next Steps

The AP Subgroup plans to finalize its selection of agents for testing in ACTT3 by Sunday, May 4, and will then recommence the prioritization process in search of high-priority agents for testing under the *De Novo* ‘Gold Standard’ MP, which it will begin drafting after agents are selected for prioritization. The AP Subgroup will need to select agents before it can begin specifying details for the *De Novo* MP, which it anticipates having finalized by July 2020 (FNIH has confirmed that ACTIV can solicit external experts to assist in writing the *De Novo* MP).

The MP Subgroup will reevaluate its outline of the ACTT3 MP design based on FDA’s (b) (4) approval and the AP Subgroup’s final set of prioritized agents for potential repurposing. Then it will pivot to begin drafting its *De Novo* MP, with input from representatives of both REMAP-

COVID and I-SPY-COVID. (FNIH already possesses the REMAP-COVID protocol and hopes to receive the I-SPY2-COVID protocol this weekend.) While developing its *De Novo* MP, it will be crucial for MP Subgroup members to confirm that sponsors of all selected molecules are committed to providing adequate supplies if their drug should become SOC.

Meeting Schedules

Starting next week, the AP Subgroup will meet on Mondays, Wednesdays, and Fridays, whereas the MP Subgroup will meet on Tuesdays and Thursdays. The main TX-Clinical WG will continue to meet on Thursday afternoons. This new schedule should allow for more work time between meetings of each subgroup, although Dr. Stacey Adam clarified that ad hoc subgroup meetings may still be scheduled to supplement the above schedule when necessary.

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Timothy G. Buchman, MD, PhD, Biomedical Advanced Research and Development Authority (BARDA)

Joan Butterton, MD, Associate VP, Clinical Research, Infectious Diseases, Merck & Co.

Sylva Collins, PhD, Director of the Office of Biostatistics, FDA

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Angelo DeClaro, MD, Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)

Ruxandra Draghia-Akli, MD, PhD, Global Head, Global Public Head R&D, Johnson & Johnson

Carl Garner, PhD, VP, Global Regulatory Affairs, Eli Lilly

Keith Gottesdiener, MD, Former President and Chief Executive Officer, Rhythm

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)

Eric Hughes, MD, PhD, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)

Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke

Lisa LaVange, PhD, Associate Chair, Department of Biostatistics, UNC

Elliott Levy, MD, Senior VP Global Development, Amgen; TransCelerate Board Member

Yuan-Li Shen, Deputy Director (Acting), Division of Biometrics V, CDER, FDA

Sandeep Menon, PhD, Senior VP and Head of Early Clinical Development, Pfizer

Naimish Patel, MD, Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi

Amanda Peppercorn, MD, Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)

Dionne Price, PhD, Director, Division of Biometrics IV, CDER, FDA

Michael Proschan, PhD, Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

Daniel Ruben, PhD, Division of Biometrics IV, CDER, FDA

Peter Stein, MD, Director of Office of New Drugs, CDER, FDA

John Young, PhD, Global Head, Infectious Diseases, Roche

INVITED PARTICIPANTS

Christine Colvis, PhD, Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer, NIH*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Senior VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP, Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Sam Bozzette: 24:41

is it possible to view/hear a archived version of this talk?

Timothy Buchman: 25:32

I can obtain the slide deck if that wil help.

Ruxandra Draghia-Akli: 25:42

it would be great!

Sam Bozzette: 26:19

that would be great

Sam Bozzette: 42:45

share the concern about capacity of the various sites and networks - there are dozens and dozens of studies already ongoing. Don't know the whole landscape but do know that the vast majority of the ~60 CTSAs are already committed

Timothy Buchman: 01:00:14

Thank you as always to our leaders!

A Potential Public-Private Collaboration to Rapidly Respond to the Threat of COVID-19 and Future Pandemics

Introductory Call (Invitation Only)

April 3, 2020, 9:00 – 11:00 am ET

April 4, 2020



This meeting summary was prepared by David Frankowski, PhD, and Lucas Smalldon, MA, Rose Li and Associates, Inc., under contract to the Foundation for the National Institutes of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH.

Key Action Items

Key Decisions

FNIH will establish a rapid action working group (WG) in each of four Focus Areas (summaries below) identified during this meeting. Each WG will develop an action plan detailing how a COVID-19 public-private partnership (PPP) could advance progress in its designated Focus Area, to facilitate rapid response to the pandemic.

1. THERAPEUTICS – PRECLINICAL

Standardize and share methods for preclinical evaluation of candidates

Action: Establish a centralized process and repository for harmonizing and sharing methods and evaluating models

- In vitro screening – extend access to HTS facilities, especially BSL-4
- Goal is to test ALL compounds that have been in human trials, to identify potential for repurposing
- Increase access to validated animal models, especially NHPs
- Enhance comparison of approaches to identify informative assays

Considerations:

- Sharing of methods and data in an open forum that allows for assay comparison and validation
- Leveraging existing capabilities (e.g., NIH animal models)

2. THERAPEUTICS - CLINICAL

a. Prioritize candidates for clinical evaluation

Action: Establish a joint Steering Committee to rank potential candidates:

- Assemble appropriate expertise with unassailable objectivity
- Develop a complete inventory of candidates with acceptable safety profiles (start with BioCentury database)
- Set criteria for judging candidates, including scientific rationale and potential scalability
- Provide independent recommendations for prioritization of candidates, and distribute to appropriate stakeholders

Considerations:

- This must be nimble and fast to be useful
- Prioritize candidates with different MOAs, rather than multiple candidates with the same MOA
- Leverage prioritization efforts already done by others (e.g., UK)

b. Accelerate clinical evaluation of candidates with near-term potential

Action: Design and launch a master protocol platform for adaptively evaluating candidates

- Establish and openly share master protocol(s) with agreed upon endpoints, sampling and analysis
- Identify available clinical trial capacity across all participants (NIH networks, companies), provide access to different patient populations and disease stages (see topic 3 below)
- Leverage prioritization efforts to identify first-wave and subsequent candidates for evaluation
- Utilize single control arm to enhance trial efficiency

Considerations:

- Severe disease / ARDS protocol should be one area of particular focus
- Sharing of full protocols and results should be facilitated
- (b) (4), (b) (5)

3. CLINICAL TRIAL CAPACITY**Maximize clinical trial capacity and effective utilization**

Action: Establish a coordination mechanism for networks and organizations with clinical trial capacity

- Share capacity and capabilities, including specialization in different populations / disease stages
- Track incidence across sites and project future capacity
- Develop methods to expedite trials

Considerations:

- Leverage infrastructure and expertise from across NIH networks, including NIAID networks, NHBLI PETAL, SIREN, CTSAs, etc.
- Repurposing clinical trial capacity will not be trivial for all networks, and may need facilitation

4. VACCINES**Create a collaborative framework for advancing vaccine development**

Action: Create a collaboration dedicated to sharing insights into natural immunity and vaccine candidate immune response.

- Mapping of epitopes and development of assays
- Protocols for sampling and immunological analyses and reagents
- Clinical data on immunological responses and endpoints, to enable meta-analysis of correlates of protection

- Engagement with regulators on surrogate endpoints for clinical evaluation

Considerations:

- Enabling work happening already from JnJ, Merck, Vir, NIAID VRC, and others
- Vaccine development efforts need to stay closely informed by work on the pathway to manufacturing at scale

Immediate Next Steps

- Participants will nominate experts from their organizations to join the four planned WGs by sending names to Mike Santos (FNIH).
- Participants will send to Joe Menetski (FNIH) the names of any additional organizations that they recommend inviting to join the potential COVID-19 PPP.
- Participants will send any further comments from this meeting to David Wholley (FNIH).
- Dr. Rupert Vessey (Bristol-Myers Squibb) will circulate to FNIH who forward to participants a link to BioCentury's database on the COVID-19 research landscape. [Note: the URL is <https://www.biocentury.com/coronavirus>]

High-Level Meeting Summary

In response to the emergence and rapid spread of the SARS-CoV-2 virus and of the Coronavirus Disease 2019 (COVID-19), this meeting convened leading members of the National Institutes of Health (NIH), the biopharmaceutical industry, the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA), and academic researchers to discuss potential opportunities to establish a new biomedical research PPP to respond rapidly to COVID-19 and to plan for future pandemics. Participants explored ways to accelerate development and regulatory approval of therapies and prophylactics—especially vaccines—for COVID-19; a separate meeting with a different group of experts will convene to discuss diagnostics.

Below are detailed summaries of discussions around each of the Focus Areas. Appendix A provides a list of participants.

Discussion Summaries

At several times during the discussions, Dr. Anthony Fauci, Dr. Clifford Lane, and Dr. Larry Corey drew parallels between past efforts to combat HIV and the contemporary challenges of confronting the spread of COVID-19. They noted that some of the strategies used against HIV may provide a fruitful starting point for developing strategies against the COVID-19 pandemic. Indeed, the unprecedented level of collaboration and data sharing that characterized the fight against HIV were identified as an urgent precondition for the success of all potential approaches to COVID-19 discussed during the meeting. Drs. Dolsten, Stoffels, and Woodcock echoed the theme of needing to collaborate to meet both immediate and longer-term aims, but

also the need to focus on a limited number of aims that can be implemented quickly and efficiently.

Focus Area 1: Therapeutics: Preclinical Development

Participants discussed the need for preclinical disease models that can accelerate identification and screening of compounds for potential entry into clinical trials. Screening may utilize animal models as well as in vitro cell-based and non-cell-based assays to identify both repurposed and novel candidate drugs.

Participants agreed that all screening efforts should adopt certain parameters to yield maximum value: (1) companies should agree to standardized protocols and unprecedented levels of preclinical data sharing, both to accelerate progress and to avoid duplication of efforts; and (2) preclinical screening of candidate compounds for efficacy against COVID-19 should prioritize tests of already-approved drugs with known safety data for potential repurposing. Specific parameters for animal models and assays as well as ongoing preclinical efforts were also discussed.

Animal Models

Participants noted that the PPP should focus on the most relevant animal models in order to forecast therapeutic efficacy in humans. NIAID is developing animal models through both its intramural and extramural research efforts. However, many animal models in use by the field lack immunological relevance to humans; nonhuman primate models may provide the most (though not universally reliable) immunological relevance. Because various animal models are immunologically complex and have uncertain biological relevance, regulators should be cautious when using animal model data as a strict approval filter. A central clearinghouse for animal model data is highly desirable.

Assays

To conduct preclinical screenings in a robust and scalable way, companies should access not only relevant animal models, but also well-validated assays, including some that require Biosafety Level (BSL)-3 and -4 preclinical facilities to perform. NIH laboratories such as the Rocky Mountain Laboratories and the NIAID's Integrated Research Facility in Fort Detrick, Maryland, as well as laboratories in Europe (e.g., a BSL-4 facility at the University of Leuven in the Netherlands), are examples of BSL-3 and -4 facilities.

Ongoing Preclinical Efforts

CALIBR, the drug development division of Scripps Research, is actively conducting preclinical screening of candidate therapeutics, including for repurposing, in response to the SARS-CoV-2 pandemic.

Focus Area 2: Therapeutics: Clinical Development

Although preclinical screening of candidate compounds is vitally important, clinical testing is critical, and many compounds are eligible to enter clinical trials. NIH and large pharmacos are being bombarded with requests to support development of new therapeutic drugs, biologics, and vaccines, and FDA is currently deluged by Investigational New Drug (IND) applications. Participants discussed the need for a system that helps the field to prioritize candidate drugs in a rational, credible, and swift way.

There was also strong support for developing a master clinical trial protocol that would facilitate the rapid execution of trials and evaluation by regulators (including potentially basket trials and adaptive trial designs).

Lessons from HIV for a Consensus Prioritization System

FDA, NIH, and pharmaceutical R&D organizations are “completely swamped” by interested parties who want to have their drug studied. While some (such as FDA) have set up triage units, the danger remains that we will end up with a lot of disconnected, small trials rather than a coordinated effort that brings forward the most credible candidates. Some more formal system of prioritizing therapeutic candidates, and sharing the relevant data, is critical. A consortium of pharmaceutical companies has already begun providing a publicly available inventory of current development efforts in collaboration with the science news publisher BioCentury.

Past HIV efforts may provide a blueprint for proceeding. Dr. Fauci noted that the National Institute of Allergy and Infectious Diseases (NIAID) previously established a prioritization system for candidate HIV therapeutics. The system established a diverse group, including representation across multiple NIH Institutes and various biopharmaceutical companies, that was responsible for prioritization decisions and for developing master protocols to accelerate testing of candidate therapeutics while generating easily comparable and interpretable data. Dr. Lane stressed that the system demonstrated the importance of advance agreement by all parties on prioritization criteria, in order to avoid any potential conflicts of interest or counterproductive disputes over decisions.

Considerations for Future Prioritization Decisions

When assessing and prioritizing candidate COVID-19 therapeutics, it will be critical to consider target population and therapeutic mode (e.g., targeting the virus, targeting inflammation, protecting healthy organ functioning). Another key consideration should be feasibility of large-scale manufacturing and distribution of the candidate therapeutic.

Establishing a single-trial protocol, potentially for basket trials, with a single Institutional Review Board (IRB) approval, established surrogate markers of efficacy, and an overarching DSMB would help to facilitate rapid trials of prioritized compounds that generate comparable outputs for assessment by regulatory agencies. Dr. Woodcock noted that a master protocol approach would be particularly useful for drugs that address cytokine storms and antiviral treatments for

hospitalized patients. The regulatory framework for this approach should be harmonized across both FDA and EMA.

Participants discussed establishing a 'Joint Steering Committee', composed of representatives from diverse institutions, with the authority and scientific credibility to issue prioritization decisions for candidate COVID-19 therapeutics. This Joint Steering Committee could also leverage data generated by clinical trials prioritized in the UK and by NIAID's clinical trials network to inform its prioritization decisions.

International Prioritization Efforts

Dr. Mene Pangalos notified participants that the UK has established two independent review panels of academic experts, regulators, and representatives of the biopharmaceutical industry. One panel has evaluated and prioritized the top eight existing therapies, which are already approved or in late-stage development, for entry into drug repurposing trials for COVID-19. The other panel will evaluate and prioritize candidate COVID-19 vaccines. As UK government-funded entities, these two independent review panels are authorized to issue binding prioritization decisions. Testing is expected to begin next week and may already have begun for hydroxychloroquine and azithromycin.

Coordinating and standardizing prioritization of candidate therapeutics globally would accelerate identification and approval of effective therapeutics and would eliminate duplicative efforts such as redundant testing of a single mechanism of action (MOA). It would also relieve the burden on regulators by decreasing the overall number of IND applications and would help to avoid inundating clinical trial sites with requests to run trials as they are overwhelmed with treating COVID-19 patients.

Focus Area 3: Building and Coordinating Clinical Trials Network Capacity

Once therapeutics are prioritized by the Joint Steering Committee, an established infrastructure to test these therapeutics in clinical trials will be urgently needed. Many normal clinical trial sites are currently overwhelmed with treating COVID-19 patients, which may lessen their capacity. Participants identified both public and private networks that could be mobilized to expand resources and share data. One participant noted that a particularly important gap is developing trials for patients with severe disease, e.g. Acute Respiratory Distress Syndrome (ARDS).

Potential Trial Networks

Various NIH Institutes, such as NIAID, the National Cancer Institute (NCI), and the National Heart, Lung, and Blood Institute (NHLBI), have existing clinical trials networks that could be integrated to achieve greater speed and statistical power in evaluating candidate therapeutics for COVID-19. NIH also has an emergency room clinical trials network—SIREN—that could be leveraged to recruit COVID-19 patients who arrive in emergency rooms seeking initial treatment. Many clinical sites within the NIH clinical trials networks are also part of the National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science

Awards (CTSA) network. All of these existing networks could potentially be linked together to form a “network of networks.” That network would enable more rapid, rigorous testing of candidate therapeutics for COVID-19 through clinical trials, potentially under a single master protocol that supports basket trials and shared control arms.

Company representatives also expressed a willingness to share resources, including clinical trials and manufacturing infrastructure—even in support of advancing candidate compounds developed by competitors. It could be useful to assemble an inventory of available NIH and company resources, especially regarding clinical trial capacity amid COVID-19 patient loads,

Expectations for Data Sharing

As clinical trials are conducted, all protocols and results must be shared in real time across the COVID-19 PPP in order to eliminate duplication of effort and accelerate progress (e.g., by synergizing endpoints for consistent readouts to assist regulators). From the regulatory standpoint, it will also be important to convey contexts of use for candidate therapeutics, such as therapeutic aim (e.g., prevention of infection versus symptom treatment in severe patients) and targeted disease stage. Regulators would also support master protocols governing COVID-19 clinical trials, and Dr. Guido Rasi noted the potential value of achieving modular approval (e.g., of certain families of therapeutics or approaches) to accelerate approval of novel COVID-19 therapies.

Although further discussion is needed to identify an institution that could establish a (b) (4), several participants suggested (b) (4). Companies currently working on similar efforts include (b) (4).

Focus Area 4: Collaborating on COVID-19 Vaccine Development

Protective vaccines for COVID-19 are urgently needed. To develop vaccines on a rapid timeline, participants identified ways to improve measurement of potential efficacy and to accelerate regulatory approval. As various vaccine development efforts proceed, investigators must also consider which approaches will be easiest to manufacture and distribute at scale. Dr. Peter Marks noted that mRNA approaches could present advantages over viral vector approaches in terms of scalability.

Surrogate Markers of Immunity

One way to accelerate vaccine development is to identify and validate surrogate markers of protection from SARS-CoV-2. A validated surrogate endpoint, with measurement data shared in real time, could speed the identification of candidate vaccines significantly compared to trials looking directly at protective efficacy. Potential surrogate endpoints could be identified and assessed by an overarching Data Safety Monitoring Board (DSMB) and an independent lab.

Dr. Roger Perlmutter described ongoing work in Seattle to study markers of COVID-19 immunity and noted that all the resulting information will be made publicly available. If data on a candidate surrogate endpoint could be aggregated across events from multiple clinical trial

networks, it may be feasible to achieve statistical significance required to validate that surrogate endpoint.

Approaches to Accelerating Regulatory Approval

An umbrella approach to vaccine trial evaluation could also accelerate regulatory approval to advance the most promising candidate vaccines. Dr. Marks noted that current approaches to vaccine development for SARS-CoV-2 span a broad spectrum that includes live viral vaccines and killed virus vaccines, as well as DNA and mRNA vaccines. Therefore, although it may be beneficial to establish some shared set of efficacy standards, the chances of achieving a one-size-fits-all evaluation standard are low. The most fruitful avenue may be to establish general principles that can be flexibly applied across vaccine approaches.

To standardize comparison across vaccine platforms, (b) (4)

However, vaccine developers are not currently coordinating efforts systematically, and such coordination is needed to accelerate progress and to achieve validation of surrogate endpoints for use across trials. Achieving consensus regarding two or three epitopes where neutralization correlates well with outcomes in early-stage disease and that could be used as a surrogate endpoint across all vaccines may dramatically accelerate COVID-19 vaccine trials. (b) (4)

plays a central role in funding vaccine development and manufacturing capacity and serves as a central repository of information related to these efforts. (b) (4) safeguards every company's proprietary information involved in vaccine development, but participants are prepared to engage in unprecedented data sharing.

Appendix A: Participants List

Francis Collins, MD, *Director, National Institutes of Health (NIH) (Session Leader)*

Christopher P. Austin, MD, *Director, National Center for Advancing Translational Sciences (NCATS), NIH*

Rick A. Bright, PhD, *Director, Biomedical Advanced Research and Development Authority (BARDA)*

Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*

Gary L. Disbrow, PhD, *Acting Deputy Director, BARDA*

Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Anthony S. Fauci, MD, *Director, NIAID, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

John Mascola, MD, *Director, Vaccine Research Center, NIAID, NIH*

David Meeker, MD, *KSQ Therapeutics (formerly Genzyme)*

Mene Pangalos, PhD, *EVP, BioPharmaceuticals R&D, AstraZeneca*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Steven M. Paul, MD, *CEO, Karuna Therapeutics; Chairman of the Board, FNIH*

Roger M. Perlmutter, MD, PhD, *EVP and President, Merck Research Laboratories*

Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*

Guido Rasi, MD, *Executive Director, European Medicines Agency (EMA)*

John C. Reed, MD, PhD, *EVP, Global Head: Research, Sanofi*

Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*

Paul Stoffels, MD, *CSO, Johnson & Johnson*

Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*

John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*

Rupert Vessey, DPhil, *President, Research and Early Development, Bristol-Myers Squibb*

Herbert (Skip) Virgin, MD, PhD, *EVP Research and CSO, Vir Biotechnology*

Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

Stephanie James, PhD, *Senior VP of Science, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

ACTIV, Therapeutics-Clinical

Working Group Meeting 4, Key Takeaways

Thursday, April 30th, 2020

Action Items

Action Items		
	Information	POC
1	Prepare documentation to show the Agent Prioritization Subgroup Review Committee's rationale for decisions in the Agent Prioritization process. It would be helpful to share about how triage process was done, compiled scoring, the commentary made, etc.	Stacey Adam / Elizabeth Kim
2	Determine writers for ACTT3 and De Novo Master Protocols	Lisa LaVange / Sarah Read and Eric Hughes
3	Subgroups follow up on appropriate next steps determined	All Subgroup Members

Key Takeaways

Agent Prioritization

- How does scoring process change with focus on (b) (4), (b) (5) Needs further discussion
- Important to note that criteria scoring system does not make prioritization of agents final. Expert opinion and insight will of course be strongly considered/outweigh the scoring numbers if there's disagreement. The scoring system facilitates further discussion.
- Discussion regarding anticoagulants – doctors in the field seeing aggressive micro-thrombosis. The team paying special attention to agents that could help address for this first wave of review.

Master Protocol

- Discussion on putting agents in early screening. Concern that the agents that we are moving forward do not have a high probability of success and may not be suited to a large confirmatory study. Despite communication with the Agent Prioritization team and their best efforts to identify that type of compound.
- Potential need to have more confirmatory patient population later after initial testing of current agents
- Potential ability to address some of the concerns expressed about agent readiness by fine tuning the ACTT3 futility analysis

Moving forward

- Agent Prioritization
 - Refine agent prioritization process for round 2
 - By tomorrow, 5/1 or later this weekend, have final list of agents that meet ACTT3 design
 - Re-start prioritization effort for *de novo* master protocol effort
- ACTT3 outline

ACTIV, Therapeutics-Clinical Working Group Meeting 4, Key Takeaways

Thursday, April 30th, 2020

- Master Protocol group has basic outline for ACTT3. Outline needs to be re-evaluated in the context of the Remdisivir approval and agents put forth by agent prioritization subgroup.
- De Novo master protocol
 - Begin discussions/assessment for *de novo* master protocol
- Next week, REMAP COVID will speak to the group. We've reached out to I-SPY-COVID.
 - We are in possession of REMAP COVID protocol and trying to obtain I-SPY protocol.

Chatbox

From Sam Bozzette to Everyone: 02:19 PM

is it possible to view/hear an archived version of this talk?

From Timothy Buchman to Everyone: 02:20 PM

I can obtain the slide deck if that will help.

From Ruxandra Draghia-Akli to Everyone: 02:20 PM

it would be great!

From Sam Bozzette to Everyone: 02:21 PM

that would be great

From Sam Bozzette to Everyone: 02:37 PM

share the concern about capacity of the various sites and networks - there are dozens and dozens of studies already ongoing. Don't know the whole landscape but do know that the vast majority of the ~60 CTSA's are already committed

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics elevated for its consideration.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has activated (b) (4) (104 sites total) and has (b) (4) as of February 2, 2021. (b) (4) will imminently reach its halfway mark of (b) (4). The ACTIV-2 team will likely submit (b) (4) without a pause, assuming the agent appears to be safe. (b) (4) teams are beginning to develop the appendices for their agents to enter ACTIV-2 version 5. Dr. (b) (4), (b) (6) noted that multiple ACTIV-2 study (b) (4), (b) (5) (b) (4). The ACTIV-2 team is waiting for the first patient to enroll into the (b) (4).

The ACTIV-2 team has also been working to improve outreach to the Black community to increase demographic diversity.

ACTIV-3

ACTIV-3 has activated 39 sites and (b) (4). Two of the activated sites are open for enrollment into the (b) (4) PI as of February 2, 2021. The ACTIV-3 team is working to open further (b) (4), and FDA is helping to activate additional sites for version 3. The ACTIV-3 team expects its DSMB to conduct a first (b) (4) when it meets on March 1. Dr. Stacey Adam will contact ACTIV-3 leaders about onboarding (b) (4).

Topics for Discussion

Vaccination (b) (4) Update (ACTIV-2)

(b) (4) has reported that it no longer possesses any clinical trial-labeled doses of its vaccine, and therefore will not be able to supply the proposed (b) (4), although (b) (4) representatives have expressed support for the study concept. Dr. (b) (4), (b) (6) noted that at (b) (4) suggestion, ACTIV has submitted a request for (b) (4) and that it would be useful to update Dr. (b) (4), (b) (6) in case her involvement may help ensure that FDA grants the request. Dr. (b) (4), (b) (6) emphasized that only (b) (4) and asked Dr. (b) (4), (b) (6) to update Dr. (b) (4), (b) (6) whenever possible. Dr. (b) (4), (b) (6) will contact (b) (4), (b) (6) representatives to arrange backup plans to obtain supplies of vaccine from (b) (4) and Dr. (b) (4), (b) (6) will contact (b) (4), (b) (6) representatives to gauge the possibility of obtaining (b) (4), (b) (6) vaccine supplies for the study.

Speed is a critical consideration because the ACTIV-2 team wants to include in the vaccination (b) (4), (b) (5) as many patients as possible who were originally enrolled to the (b) (4), and these patients will continue to drop out of the enrollment window as time elapses. Mr. (b) (4), (b) (6) offered to raise these issues to the ACTIV War Room and to discuss the possibility of engaging (b) (4). Drs. (b) (4), (b) (6) agreed to this strategy, noting that if these issues are unresolved before the next ACTIV Leadership Team meeting (February 17), then they can be discussed further in that forum.

Discussion

Dr. (b) (4), (b) (6) asked whether data are available from Phase (b) (4) vaccine trials showing antibody response in (b) (4) individuals after vaccination and comparing reactivity to the first and second doses of vaccine between (b) (4) individuals. Dr. (b) (4), (b) (6) will determine whether these analyses have been completed and report back during the next TOC meeting.

Fostering a Combined Analysis of mAbs Across Companies

The TOC discussed potentially facilitating a combined analysis of data from across ACTIV-2 and company trials (b) (4) in order to identify (b) (4), (b) (5)—symptom- or (b) (4), (b) (5)—that could be used in future clinical trials. (b) (4) has already been contacted, but the ACTIV-2 team would likely require assistance (e.g., from (b) (4)). Dr. (b) (4), (b) (6) suggested first attempting to reach (b) (4).

Updates on (b) (4), (b) (5) Trial (ACTIV-6)

ACTIV representatives have held discussions with several groups (b) (4) to begin planning a proposed ACTIV-6 study, with (b) (4) as the potential lead organization. The TOC has also been proposed to serve as the study's lead governing body; several TOC members tentatively endorsed this proposal, although they acknowledged that further details are needed before that decision can be confirmed (e.g., trial governance and agent selection parameters).

New York Times Article on Therapeutics Development

Mr. Wholley reported that leadership of NIH and FDA—in response to a recent *New York Times* [article](#) implying that the federal government and biopharmaceutical industry have done little to pursue therapeutics against COVID-19—are organizing proactive efforts to communicate to the public, through various channels, all the therapeutic-centric activities undertaken by ACTIV. Dr. Adam, with the support of colleagues from Deloitte, has provided information on ACTIV studies to inform these efforts. The *New York Times* reporter, Carl Zimmer, agreed to update the online version of his piece. Dr. Smith noted that the ACTIV-2 team has drafted a communication in the form of a “letter to the editor” which he will send to Mr. Wholley.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Samuel Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Elizabeth Church, PhD, Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Ann Eakin, PhD, Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)

Emily Erbeling, MD, MPH, Director, Division of Microbiology and Infectious Diseases, NIAID, NIH

David C. Goff, MD, PhD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, Global Health Science Advisor, NIAID, NIH

James P. Kiley, PhD, Director, Division of Lung Diseases, NHLBI, NIH

Peter Kim, MD, Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH

H. Clifford Lane, MD, Deputy Director for Clinical Research and Special Projects, NIAID, NIH

Jens D. Lundgren, MD, Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT

Gilbert (Lynn) Marks, MD, Senior Adviser to BARDA, Office of the Director

James D. Neaton, PhD, ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

Erica Ollmann Saphire, PhD, Professor, La Jolla Institute for Immunology

David (Davey) Smith, MD, Professor of Medicine, U. California, San Diego

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, Director of Special Programs Staff, Office of New Drugs, FDA

William Erhardt, MD, Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants

Ashley Parker, PhD, Health Science Policy Analyst, NIH

Austin Van Grack, MS, Committee Coordinator, Social and Scientific Systems

STAFF

Stacey Adam, PhD, Director, Cancer, Foundation for the NIH (FNIH)

David Wholley, MPhil, Senior Vice President of Research Partnerships, FNIH

Helen Q. Chen, Consultant, Deloitte

Evan Appell, Consultant, Deloitte

Hana Nasr, MPH, Consultant, Deloitte

Lucas Smalldon, MA, Writer, Rose Li and Associates, Inc.

Appendix B: Chat Transcript

jens lundgren: 22:40

do we have data from phase 3 for Moderna / Pfizer for those with prior antibody positive?

ann eakin: 30:36

Marina Kozak is the PCT lead

David Goff, NHLBI: 34:15

It makes sense to me. Collaboration and coordination of governance makes sense.

David Goff, NHLBI: 37:45

completely agree with Sarah and Cliff

Currier, Judith, M.D.: 42:29

<https://www.nytimes.com/2021/01/30/health/covid-drugs-antivirals.html?smid=tw-share>

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 10, Key Takeaways

Tuesday, April 28th, 2020

Action Items

Action Items		
	Information	POC
1	Master Protocol Sub Group merged meeting with Clinical Trial Capacity Working Group on Thursday, 4/30 to have broader discussion on needs	Master Protocol Sub Group
2	Query Michael Proschan with questions regarding ACTT: • Safety/futility • Randomization tool required	Michael Proschan / Stacey Adam/Lisa LaVange
3	Coordinate meeting with REMAP-COVID and get permission to share protocol	Elliott Levy / Stacey Adam
4	Coordinate meeting with I-SPY-COVID. Continue to try and acquire I-SPY protocol	Stacey Adam
5	Moving forward, Master Protocol Sub Group should remember to follow up on decision regarding: • Formal stopping rule for harm • Definitions, particularly “medical care” and “not regarding medical care” – making this objective • Death as secondary endpoint vs. having 1-point worsening on 8-point scale.	Master Protocol Sub Group
7	Need to decide who will write ACTT3	Lisa LaVange / Sarah Read/ Stacey Adam

Key Takeaways

- Consensus reached to interim analysis at 33% and 67%.
- Consensus to use the CDL method at the 67% mark for an unblinded sample size evaluation
- Consensus that more learning is needed from ACTT – such as why do they not have a formal stopping rule, and what randomization tool was required?
- Key decisions/further analysis needed made moving forward:
 - Formal stopping rule for harm
 - Decide how to define “medical care” and “not requiring medical care” for objectivity
 - Using death as a secondary endpoint vs. having a 1-point worsening on the 8-point scale. This decision will be tabled until we receive the list of agents for wave 1 from the Agent Prioritization Sub Group.
 - Need a better understanding, in secondary analysis, of the people who are in hospitals for other reasons and then get COVID-19. What are the segments of people in these groups?
 - Will be important to build into the Master Protocol a means to deploy vital status if unable to reach patient or family member, as is currently done routinely in cardiovascular trials and some cancer and transplant trials.
- Next steps:
 - Sub-Chair and Co-Chairs to decide whether Master Protocol Sub Group will have meeting tomorrow, 4/29.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group Working Group Meeting 10, Key Takeaways

Tuesday, April 28th, 2020

- Sub Group to have joint meeting with Clinical Trials Capacity Working Group on Thursday, 4/30.
- Ideally, Master Protocol Sub Group will begin incorporating final list of first wave agents during meeting this Friday, 5/1. *(Post meeting note: This will likely be delayed until Monday.)*

Summary of Decisions To Date, and Clarifying decisions

- Summary of Decisions from last week and this week thus far (See Meeting Guide slide titled “Design Considerations for ACTT3”)
- Decisions made yesterday (See Meeting Guide slide titled “Sample Size and Power for Add-on Protocol slide & Interim Analysis”)
- Reaching group consensus regarding unblinded sample size re-estimation
 - Sub-Chair: Simple and cleaner to have a single interim analysis. We agreed to try to have a power to detect a recovery rate of 1.25. That’s a little over 2,000 patients and is a long time to wait.
 - Like the idea of 33% for the idea of futility as much as anything else.
 - We can hold on the sample size re-estimation until the 67% point.
- WG member responses:
 - If there is a stopping rule for futility, does there have to be one for harm? Obviously if a drug is harmful, it’s futile as well.
 - WG needs to answer these questions. ACTT2 doesn’t have a formal stopping rule for harm.
 - WG member argues for one. It could be that there’s an adverse effect on the disease course itself which you can only look at by measuring adverse effect on primary endpoint.
 - It’s usually a good idea with a Master Protocol to have a blanket issue (lab values going too high or too low, etc.). Depending on the agents, we may have to look for a side effect or something specific for agents. We didn’t decide on futility stop. We can make this liberal. It depends on our philosophy – if we only want drugs that have solid power to show something, or do we want to be more conservative and have a real high probability of success with the drug?
 - 33% - for safety, futility, efficacy and 67% - enact the CDL method and judge for sample size
 - Be open minded for 33% given there may be a transformational effect in one of the arms. Do we have some sort of rule for transformational efficacy at 33%?
 - 33% will include a stopping for efficacy. We just won’t do a sample size test at that time.
 - Proposal is to allow early stopping for efficacy at 33% (for whopping effect) and the CDL method at 67%. We acknowledge that stopping at a third of the way through will be really difficult.
 - Details of the stopping rules have to be carefully pre-specified.

Tuesday, April 28th, 2020

- The two that we haven't specified are the futility and safety. ACTT2 had no safety boundaries.
- Sub-Chair would like to hear from Mike why ACTT did not put in the safety boundaries.
 - In ACTT1, may not have thought it was necessary for Remdesivir.
- Futility Analysis decision
 - For futility, FDA usually uses 20% or less conditional power. Sandeep was asking yesterday about how that would translate to a clinically meaningful delta.
 - Worry is that the conditional power, will need to back translate into the treatment effect and have that be vetted out with the clinicians. Sandeep is fine with using the CDL method but want to make sure we back translate into the treatment effect. This can be done. It's just a p-value combination approach. This needs to be agreed by the medics on the call because we don't want to get into a p-value-based or 20% conditional power rule that no one's able to interpret.
 - ACTT2 doesn't spell out the futility value either. Sub-chair would like Mike to weigh in on this.

Secondary endpoints

- WG member: Going to the secondary analysis is an easy one. They have days on ventilator and days in hospital. Trouble is that people get readmitted and death. Most people have gone to hospital-free days and ventilator free days out of ~28 as an alternative.
- The more difficult is regarding the primary endpoint. Hospitalized not requiring supplemental oxygen/no longer requires ongoing medical care – this is really tough.
 - John made this point yesterday that we need to decide what “not requiring medical care” means. How do we make this objective?
 - If you're still requiring home oxygen, are you really fixed?
 - It strikes WG member that it's okay to have oxygen at home, and you're at an endpoint. But it's not okay to be at the hospital and have oxygen.
 - Co-Chair: We are not changing for consistency. These are used by ACTT1 and ACTT2 and a number of pharmaceutical trials. Would favor keeping these for consistency.
 - Another WG member: For the primary endpoint, definition is adequate. These are patients who have reached a point in their treatment course that separate them from everyone who is still in the hospital, on oxygen, getting intensive care, etc. It's a meaningful clinical endpoint.
 - Another WG member: Okay with keeping this.
 - WG member: Outcomes may depend on region as well. There are probably different groups when they're sick enough to go to the hospital.

Tuesday, April 28th, 2020

- Suggestion to put more definition on those stuck in the hospital but not requiring care. Should specify that they're not requiring care for COVID-19. Reports of people who fell and fractured something and then it turns out that they're also PCR-positive. We want to be clear that they're stuck in the hospital for something other than COVID-19.
 - This is a grey area. In ACTT, says requires care for COVID-19 "or otherwise."
 - We may be stuck with this, but we need to understand who is in those groups. This could be part of a secondary analysis to get more detail on people who are in hospital for other reasons and then got COVID-19.
 - We need to be more specific than that on what routine medical care means if we're trying not to be subjective.
- Are people okay with leaving death as a key secondary endpoint?
 - WG member: Okay with this. Immunomodulators if you are using – they may have situations that are tricky. Would defer to medical colleagues.
 - Will we have enough deaths to treat it as a co-primary endpoint?
 - Would have a hard time powering for this.
 - Alternative to death would be a 1-point worsening on the 8-point scale. Other sponsors seem to be using this as a primary endpoint. So, you'll have more events if you include transition to more intensive ventilatory support.
 - This makes a lot of sense if we can put death as a secondary endpoint.
 - Vote is to keep this simple.
 - What would be advantage of 1-point over a 2-point change?
 - It's in the other direction.
 - Would the 1-point or 2-point be at a particular time period? Worry is that if some patients are on the cusp of progressing, you may get the drug, you may progress within hours and recover. A 1-point change may be too difficult to really reflect efficacy.
 - From stats, it does make sense to have a bit more correlated endpoint here as a secondary.
 - So, the recovery is at day-29. Would the 1-point difference be from the beginning to day 29?
 - These patients are unstable on admission often, and there's a likelihood that some would progress before reasonably experiencing any benefit from the drug. So, at a milestone timepoint, though we don't have a basis for picking a particular timepoint, may be more reasonable.

Tuesday, April 28th, 2020

- Worry that people could deteriorate because drug may not kick in or kick in at different rates. And for some treatments, they make you worse at least initially. It's not uncommon in infectious diseases for people to get worse before getting better even if it's an effective drug.
 - Given an MOA, don't think we will see a rapid lysis phenomenon. Immunomodulators will bring complicated changes, and it's hard to predict whether they will be helpful or harmful at this point. To capture likelihood of harm of drug with a single measure is unlikely, need to structure it so it's a true reflection of the effect of the drug. That's my concern with looking at 1-point deterioration at any point in the time scale.
 - This decision needs to be tabled until we know the agents.
 - Would be helpful to get perspective from the ACTT1 team and understand the challenges with the measures we are sticking with.
- For other discussion, let's wait to get feedback from ACTT and see the prioritization of agents.

Clinical Trial Capacity Workgroup Suggested Innovations to Deploy with ACTT3

- CTC WG has been discussing inventory of innovations.
- The column that they most wanted feedback on is the column they designated as "MUST-HAVE" for ACTT3.
 - They've broken this down by lifecycle of a clinical trial, planning stages, startup, enrollment and treatment, and closeout and reporting.
 - They are proposing various things that might be helpful.
- Feasibility – is the network capable of actually running ACTT3? Do we have to think about ways to help sites get ready/recruit additional sites?
- Site selection Criteria and Site Resourcing – these are assessments that CTC WG will have to do for us to place ACTT3 appropriately
- Questions and Feedback from the WG:
 - Sub-Chair: Is this intended to be used one-site at a time or for a network of sites? Emails from 3 networks are coming differently to Sub-Chair. Unclear if the surveys are a single site tool or a network tool.
 - Stacey Adam: They are doing a bit of both. They are trying to focus at the network level. Networks can mean a number of different things. They just sent out the survey yesterday. Francis Collins distributed it to 60 networks and some individual sites, larger sites. The main focus should be on networks in the beginning.
 - CTC WG Members: There should be two separate surveys. One for network leaders, who then distribute another survey to sites separately.
 - For this exercise, we shouldn't be terribly ambitious. There isn't time to put in very innovative methodologies. The rows with a "yes" in them are basic blocking and tackling. The other items aren't critical for this study.

Tuesday, April 28th, 2020

- The tools they proposed for “tracking site status” are widely but not universally used and are not necessary. They are “nice to have.”
- Standardization:
 - NCI has standardized all their sites (b) (4). ACTG has also standardized to (b) (4).
 - It would be simpler to standardize on one EDC system for the entire study if feasible. Most sites use (b) (4). If NIH is comfortable with this, it should be standardized in one system.
 - Don’t think we can have more than one with the timelines we are looking at.
- “Investigator Portal” – “nice to have”
 - (b) (4) is not being used. It’s not something that’s available for ACTT.
- Things in column H are identified in ACTT1, but we don’t know what was used exactly the same for ACTT2.
- Assume there is an adequate monitoring scheme for ACTT1 and ACTT2 unless indicated otherwise.
- What randomization tool does NIH use normally?
 - Patient follow up - We’ll want to make sure there are procedures in place, so every randomized patients can have status followed up.
 - Sites will have to be able to follow up when they’re at home or if they’re deceased, follow up with their family.
 - It’d be good to know what they required in ACTT for this, what’s been put in place at the site.
 - Would also want other means to deploy vital status if unable to reach patient or family member. Need to build into protocol and consent. This is done now in cardiovascular trials and some cancer and transplant trials as a routine matter.
- “Integrated platform” – “nice to have”

Recap and Next Steps

- If there’s anything else that Sub Group members think of and want to address, please bring it up for discussion.
- Need to discuss who will write ACTT3.
 - For a large portion of writing ACTT3, need to know what the agents will be to fill in the protocol. Most of the protocol could be used as is, or you need to know what the agents are.
 - Sub-Chair will update the statistical portion of the draft ACTT3. Will leave a question mark for the safety and futility stopping.
- Moving on to *De Novo* ACTIVE Master Protocol

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group Working Group Meeting 10, Key Takeaways

Tuesday, April 28th, 2020

- This will take a lot more work. The sooner we can start talking about it the better.
- We could start brainstorming *de novo*.
- We decided yesterday that reassessing REMAP-COVID was on the table. We also learned that there's an I-SPY-COVID.
 - Both have attribute that we think would be beneficial. Would it be helpful to have members of those groups come and present to this group? Yes.
 - FNIH hasn't been able to acquire the I-SPY-COVID protocol.

Chatbox

From menons09 to Everyone: 01:10 PM

Ok with 33% for IA but it should be only for futility. Efficacy if there is only transformational effect. Need to define what transformational looks like..

Also for Sample Size Re-estimation not recommended to do it with 33% enrollment. Need at least 50%..

From Peter Wung to Everyone: 01:22 PM

I agree with the keeping the primary endpoint as is, although it may be worthwhile to look at the regional differences, if there is no plan to stratify by country.

From menons09 to Everyone: 01:24 PM

It will be stratified by site Peter, so we should be good.

From (b) (6) to Everyone: 01:25 PM

I would vote for promoting death

[Additional comment – apologies, missed this in copying and pasting over!]

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group Working Group Meeting 9, Key Takeaways

Monday, April 27th, 2020

Action Items

Action Items		
	Information	POC
1	Provide ACTT1 readout (when available)	Michael Proschan
2	Continue discussion with ACTT team regarding timing of ACTT1 and ACTT2 with regards to potential timing for ACTT3	Sarah Read
3	Redistribute ACTT2 Section that mentions stopping/safety rules (<i>Done during meeting from Stacey</i>)	Stacey Adam
4	Provide updated FDA guidance on endpoints	FDA WG Members
5	Provide latest REMAP COVID for Master Protocol Working Group to review (when available)	Stacey Adam

Key Takeaways

- Group consensus on 1.25 goal, sample size of about 2,066 patients. The implication is that instead of the 400 recoveries for comparison, it would take 723 – almost double the recoveries.
- We will use the Chen, DeMets, and Lan approach for an unblinded sample-size re-estimation, and the “CDL” method is supported by FDA experts in the working group.
 - FDA experts also suggested having a single interim analysis at 50% instead of having 2 interim analyses at 33% and 67% (using the CDL method at 67%).
- WG consensus on need to pursue boundaries for safety/stopping rules assuming master protocol expands beyond antivirals, using the Pocock method for boundaries was suggested
- WG consensus to revisit REMAP-COVID as a potential construct for the *de novo* protocol
- Need for more information from ACTT1 readout, FDA guidance on endpoints, and target list of agents from Agent Prioritization Working Group
- Need to discuss secondary analyses at next meeting

Overview of Last Master Protocol Meeting and Discussion

- From Sub-Chair Lisa LaVange:
 - On Saturday afternoon, worked on sample size and power and interim analysis
 - It seems to be the case that Standard of Care (SoC) will vary by site. It is described as a local SoC per written policies/guidelines per treatment of COVID-19. That local written SoC is permitted to go on in this trial. Prior to this, the ACTT2 final protocol said that if using something experimental/standard label that’s not written SoC, it has to be discontinued before you’re enrolled in *this* study, and there’s no waiting period.
 - SoC needs to be at local discretion but needs to be something that is written down.

Monday, April 27th, 2020

- We want to do sham placebo. We know that it doesn't make this a double-blind trial. We think there's still some merit if we had a fourth tablet pill or something else. To keep patients blinded and allow physicians to feel like they are giving something.
- We are adding on drugs on top of SoC, with the limitation that SoC is not uniform. There could be a lot of variability. It's understood that SoC is in the background.
- We are keeping randomization equal. If we do have 4 drugs instead of 3, we will probably want to have more control patients.
- If matching placebo is available for any of the drugs, we will use it.
- Randomization will be implemented in two stages: Randomize A:B:C as 1:1:1; then randomize A: placebo or B:S or C:S, all 1:1.
- Right now, for the purposes of sample size, we will assume that everyone uses the same SoC.
- Assuming the 1:1:1:1 ratio, then in terms of sample size:
 - We pulled sample size from ACTT1 and ACCT2.
 - We are assuming a ratio of recovery rates to be what's currently being assumed for ACTT1 and ACTT2: 1.35. That RRR tests for pretty big effect and doesn't require too much sample size.
 - If we wanted a second option, Elliott Levy recommended 1.25. The implication is that instead of the 400 recoveries for comparison, it would take 723 – almost double the recoveries for comparison.
 - The last version of the ACTT protocol said that the percentage of patients that would recover is 70%.
 - This is at 85% power, log rate test, alpha=0.05.
 - For 4 arms, we would need to get more patients and recoveries.
 - Using the 70%, if we go with first option – to detect 1.35 – our sample size would be 1,142 patients.
 - If we go to the 1.25, we are looking at 2,066 patients.
 - Do we really want to require a big signal to come out of the study, power up, enroll quickly, and go for the 2,066 patients?
- Sample Size overview – Interim Analysis
 - We don't know if recovery will be 70%. When we say that it will take 2,066 patients, it assumes that nothing is going on, and recovery rates will be about the same. If we are worried about this:
 - We might hear from ACTT1 DSMB about what their blinded recovery rate is. This does not unblind the trial. We don't know if they'd be comfortable with sharing. If we hear the blinded recovery rate that can help our sample size calculation to see if 70% is the wrong number.

Monday, April 27th, 2020

- The ACTT1 and ACTT2 planned to have a blinded sample size re-estimation based on the observed recovery rate, and we can do that too. We can mimic both of them. In both, they had said they would stop at about 115 patients and check the recovery rate. This turns out to be 10% of patients in ACTT2.
 - If we hear from the DSMB, we may not need the blinded sample size re-estimation. If we recruit really quickly, we may not have enough time to use it, but better to plan and not use it, than not plan.
 - It's a logistical issue to get the data in and get it to the DSMB to decide.
- For early stopping for efficacy or futility, there would be planned possibilities for stopping at 33% or 67% - what ACTT1 and ACTT2 are doing.
- We are proposing that we go with these same stopping boundaries and spending function.
- What was more controversial was whether we should do an unblinded sample size re-estimation.
 - On Saturday, we talked about Chen, DeMets, and Lan. We didn't come down to a decision on this. We were a little nervous about overpowering.
 - We plan to stay with the primary endpoint: time to recovery.
 - Unless there's good reason to change something, we should take advantage of ACTT2 and try to leverage it.

Discussion on CDL method

- Suggestion to make sure that there is heterogeneity of SoC by site. Do we have to do stratified at least at the end to understand the implications and power?
 - Can we look into Chen, DeMets, and Lan approach?
- FDA discussed (b) (5)

 - Suggest having 50% interim analysis, in which time we do sample size re-estimation rather than having 2 interim analysis
- Sub-Chair:
 - Mike tried to use CDL in a study and got negative criticism about it, so our WG wasn't fully embracing of it and wanted to see what FDA colleagues would say this morning.
 - It's much easier than the promising zone. Some people are comfortable with a promising zone because it is so narrow.
 - Okay with 1 interim analysis instead of 2; enrollment may not go as quickly as expected.
- WG member not big fan of promising zone approach, which can have implications on power and elements of clinical relevance window
- If recovery rate effect translates into days of hospitalization, need for intensive care, need for ventilation, 25% improvement would be a very meaningful reduction on demand for hospital beds,

Monday, April 27th, 2020

ICU beds, staff caring for patients. Would encourage us to proceed forward and see if feasible to have 25%.

- Possibility to expand existing network to facilitate enrollment?

Safety/Stopping rules

- Assuming we study something other than antivirals, WG member emphasizes need to pursue boundaries for safety/stopping rules – to stop treatment if there's evidence of harm. We don't know what the effects of manipulation to immune system will have on ability to manage virus and ability to reduce persistent immune stimulation.
 - ACTT protocol doesn't put formal boundaries in for antivirals.
- Randomization is stratified by site and disease severity.
- How much does conditional power of 20% translate into the effect size? There has to be a clinically meaningful limiting line where we can walk away from the measure.
 - 20% doesn't mean anything if we don't translate.
- ACTT1 and ACTT2 aren't using CDL. There's no unblinded sample size re-estimation.
 - We would have to come up with the rules and figure out what that would be.
 - We would need a group to come up with our stopping rules if we do unblinded sample size estimation.
- Group consensus on 1.25 goal, sample size of about 2,066 patients
 - Agreement that it's an important outcome in terms of healthcare utilization that people would find this to be a substantial difference.
- Waiting on FDA guidance on endpoints
- Use of daily severity score - time to recovery is a good measure of the resource utilization?
 - Need to define what we mean by "recovery" – do we mean patient is out of hospital/no longer needs to be in hospital?
 - Hospital discharge or functional equivalent. The concept is closely linked to concept of resource utilization, and they should correspond to each other.
 - Elliott Levy suggestion to set a hazard ratio that corresponds to 25% improvement.

On Variability of Standard of Care (SoC)

- Question from WG member on number of clinics - are we staying with 100 clinics for ACTT3?
 - John Farley seemed open to the idea of adding more sites.
- Observation by WG member that when ACTT1 started, SoC was really variable, but with more trials, is optimistic that SoC is becoming more uniform than it might've been at beginning of ACTT1.

On Timing for ACTT3

Monday, April 27th, 2020

- On Saturday, the WG talked about timing – that we wouldn't go in the field until we knew readout of ACTT1, but ACTT2 would be ongoing.
- Need further discussion with ACTT team, and depends on timing of actually opening ACTT2
- Possibility to enact ACTT3 in another network still as a modification to the existing protocol, or are we limited to existing network?
 - Think anything is possible because ACTT is not being implemented at just 1 network. IDCRC is implementing but with more than a dozen additional sites added on.
 - If some reason this doesn't work out with ACTT3, we are essentially writing a standalone protocol that we can take to the ACTIV Clinical Trial Capacity Working Group.
 - Depends on the timing, what ACTT2 winds up looking like, and where it's implemented to see whether it makes sense to say with same sites at ACTT 2 or evolve it
 - From David Goff – the network that ORCHID is currently running in might be a good choice.
- Sub-Chair: We have enough decisions that have been made thus far to have at least a synopsis protocol written, until we hear what the agents are and get readout of ACTT1.
 - We will lean on ACTT2 for other decisions.
 - Need to talk about secondary analysis

Need for Careful Definitions and Endpoints

- Can we capture utilization in fine way – hospitalization-free days, ventilator-free days
 - We can report out all of the proportions and time to death.
- Regarding bias and endpoint – we should be more descriptive of our definitions of categories
- “No longer needs medical care” – needs more definition
 - Need to define what “medical care” means
 - Currently, the ACTT protocol, does opposite. Doesn't define medical care but defines reasons people are in hospital when they don't need medical care.
- Mortality should be important secondary endpoint.
- Question as to whether there can be a situation where time to recovery has advantage in one arm, but the same arm has a mortality disadvantage given heterogeneity in population and timing?
We're still trying to figure out what's the best window to assess endpoints.
 - In theory, this could happen.
 - It doesn't seem likely for an antiviral; but for immunomodulators, there's a possibility that
 - Can see situations where mortality and recovery could diverge
- There are people who are getting better but then die of other consequences of the infection.

Monday, April 27th, 2020

- Suggestion that we'd want to have ability, at a minimum, to understand the differing effects a therapy might have in earlier/late stages of disease, understanding that in later stages there may be imbalance in mortality.
 - Harm is likely to be the greatest for the most vulnerable populations with most physiologic abnormalities.
 - There might be divergence in biologics as well.

Recap and Next Steps

- We will use the (b) (5) [REDACTED], and the (b) (5) [REDACTED] is supported by FDA experts in the working group.
- FDA experts also (b) (5) [REDACTED]
- More discussion to come – ex. Concomitant therapies
- Hopefully this week, we will see ACTT1 readout which can influence discussion.
 - By the end of the week, we hope to have a good idea of first agents we'll be targeting. We gave direction to the Agent Prioritization Working Group to try and pick 3 agents that are ready for larger trial, might be ready for registration, and might have moderate to large effect. We could run in similar protocol without too much difficulty against single SoC arm.
 - There are 170 agents they're triaging.
 - Of those we think they'll score in the 10-20 range.
 - We have had contacts from:
 - REMAP-CAP and REMAP-COVID groups
 - Reasons we've decided to go with ACTT instead of REMAP-COVID:
 - REMAP-COVID was only running at 1 site.
 - RAR was something our WG not particularly comfortable with on reassignment.
 - Was predominately only focused on hospitalized
- WG consensus to revisit REMAP-COVID for the *de novo* protocol
 - State of the art features, ahead of ACTIV
 - Don't think we can study ambulatory population in same protocol as hospitalized (will have to be companion protocol)
 - They are up and running with a large number of sites entering the contracting phase. They're aggressively pursuing sites.
 - They have frequent interim analyses every 2 weeks, with potential for an arm to accrue 350-400 subjects if survives interim analyses.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group
Working Group Meeting 9, Key Takeaways

Monday, April 27th, 2020

Chatbox

From menons09 to Everyone: 02:11 PM

This is very good Lisa. Few questions: given the heterogeneity in the SOC by site, is there any plan for stratified analysis/design.

From elliottl to Everyone: 02:13 PM

would we build in stopping rules for harm?

From menons09 to Everyone: 02:16 PM

Not a fan of (b) (5) The window can be very narrow. (b) (5)

We need to do the (b) (5)

From sam bozzette to Everyone: 02:37 PM

Are planning on (b) (5))?

From menons09 to Everyone: 02:39 PM

Does the (b) (5) ratio) need to correspond to mortality as well ?

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) Co-Chairs reviewed their recent presentation to the ACTIV Leadership Group. The Agent Prioritization and Master Protocol Subgroups provided progress updates, and the WG confirmed next steps and timelines.

Leadership Group Presentation

During the ACTIV Leadership Group meeting on Wednesday, April 22, Co-Chairs from all four ACTIV WGs presented updates on progress made since program launch on April 3. Drs. Eric Hughes and Sarah Read presented on the ongoing activities of the TX-Clinical WG's Agent Prioritization and Master Protocol Subgroups. The Leadership Group responded well to the WG's overall approach of (1) prioritizing inpatients, then outpatients, then prophylaxis; (2) evaluating antivirals, host-targeted/immunomodulators, and symptomatic/supportive therapies separately, starting with approved drugs followed by clinically-ready and then preclinical agents; (3) triaging candidate compounds rapidly using general criteria (e.g., relevant mechanism of action, not already being robustly tested, available supply for testing) before prioritizing top therapies using stricter criteria and potentially a scoring system (discussed below); and (4) implementing a "hybrid approach" to master protocols, involving both a rapid-action drug repurposing protocol based on ACTT2 and a longer-term, more comprehensive *De Novo* 'Gold Standard' protocol to be developed in parallel.

Leadership Group Input/Questions

Dr. Janet Woodcock of the Food and Drug Administration (FDA) advocated strongly for splitting inpatients from outpatients in master protocols and for leveraging adaptive Bayesian trial designs with seamless transitions from Phase II to Phase III trials. The Master Protocol Subgroup's planned approach aligns well with these suggestions.

The Leadership Group also noted the possibility of testing recovered patient plasma in ACTIV clinical trials. Although the Agent Prioritization Committee (APC) has not explicitly addressed this question, several robust well-controlled trials of recovered patient plasma exist already, so the established agent prioritization criteria would likely rule out testing of this therapeutic strategy.

Agent Prioritization Subgroup Update

During earlier discussions, the Agent Prioritization Subgroup considered developing a scoring system to objectively rank agents according to its prioritization criteria. Initially, the Subgroup decided that given the vast number of compounds being considered, their varying stages of development, and the inconsistent levels of data available for each one, creating a scoring system would be infeasible. However, as the prioritization criteria have developed further, the Subgroup has begun to reconsider a scoring system focusing on the following criteria:

Preclinical data (SARS-COV2)

In vivo data in appropriate animal model (3)
 In vitro viral inhibition data in multiple relevant cell lines (2)
 In vitro suggestive mechanism data (1)
 None (0)

Clinical data (SARS-COV2)

Data from one or more small RCTs (3)
 Data from one or more uncontrolled trials (2)
 Case series, anecdotal data (1)
 None (0)

Safety

No concerns (3)
 Minor concerns (1-2)
 Insufficient data to judge (0)
 Major concern (No Go)

PK/PD

Sufficient plasma and tissue(lung) levels (3)
 Sufficient plasma levels (2)
 Insufficient data to judge (0)
 Insufficient levels (No Go)

Drug-Drug Interactions

None (1)
 Clinically Significant DDIs (0)

Availability/Scalability

Already sufficient drug in stock to begin large trials (3)
 Drug in stock with ability to manufacture enough for trial in short timeframe (2)
 Manufacturing capabilities available, but not ramped up (1)
 Not scalable at this time (No Go)

Discussion

Participants discussed whether the availability/scalability criteria should focus solely on drug supply *for trials* or also *for market distribution*. Dr. Keith Gottesdiener suggested that drugs that could not feasibly be manufactured at scale for market distribution should be ruled out. Several participants agreed, although Dr. Peter Stein noted that supply for trials may align more clearly with ACTIV's remit, which is to identify effective therapeutics. Other organizations (e.g., BARDA) will monitor ACTIV's trials and prepare the infrastructure required to scale-up the manufacture and distribution of promising agents. However, Dr. Stein agreed that if two agents are of equal merit across all other prioritization criteria, availability/scalability for market distribution could function as a tiebreaker. Participants also stressed that limited availability/scalability of a compound due to resource limitations (e.g., limited global manufacturing capacity) may be easier to overcome than limitations due to intrinsic attributes of the agent (e.g., complex biologics).

Master Protocol Subgroup Update

The Master Protocol Subgroup has begun amending the ACTT2 protocol into ACTT3 for rapid-action drug repurposing trials. The Subgroup aims to minimize changes to ACTT2, although changes will be required, based in part on which three to five agents are selected for testing. The Subgroup is discussing ACTT3 adaptations and timelines with the ACTT team and Dr. Lisa LaVange is leading the Subgroup through key decisions for the protocol.

ACTT3 will use the existing ACTT trial sites and will compare all agents to Standard of Care (SOC) and potentially to a placebo (i.e., the Subgroup assumes that agents will not have matched placebos, but if placebos are available, the trial design will be modified).

The Subgroup has been discussing potential endpoints and will likely maintain ACTT's time-to-recovery endpoint (pending ACTT2 results) but will likely reduce intensity of data collection for simplicity. Several aspects of the ACTT3 trial design cannot be finalized until more information is available. For example, speed of recruitment may preclude early termination for safety, futility, or efficacy, as well as sample size adjustment and SOC replacement. However, ACTT3 is expected to include an interim analysis to evaluate safety and efficacy. Tomorrow the Subgroup will discuss how to ensure adequate power given that endpoints might change. FDA has

stressed that these endpoints must be as objective as possible, minimizing the potential for bias in measurements.

Discussion

SOC could vary substantially by trial site, which complicates data interpretation. It is therefore vital that the Master Protocol Subgroup understand how each ACTT administers SOC; this information is being captured by the Clinical Trial Capacity (CTC) WG's survey, which will launch this week and obtain results by the end of next week.

Next Steps

A first draft inventory of candidate compounds will be circulated to the TX-Clinical WG after this meeting. The Agent Prioritization Subgroup will finalize its prioritization criteria by Saturday and plans to identify which agents will enter the ACTT3 trial by the end of next week. Selection of compounds will help the Master Protocol Subgroup finalize details of the ACTT3 amendment. The Master Protocol Subgroup will identify a writing team to draft the ACTT3 protocol, aiming to use as much language from the ACTT2 protocol as possible. During the next two weeks the TX-Clinical WG and the CTC WG will collaborate to match compounds to trial sites within the ACTT network for drug repurposing trials. All processes needed to initiate ACTT3 trials (e.g., drafting contracts, engaging the PIs, and selecting the sites to balance any overlap with ACTT2 toward the end of its accrual) should be completed by May 30. The TX-Clinical WG also expects to finalize its *De Novo* master protocol by July.

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Joan Butters, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judy Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Health R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

Yuan-Li Shen, *Deputy Director (Acting), Division of Biometrics V, CDER, FDA*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomatics Capital; Therapeutic Accelerator Lead, Gates Foundation*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

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Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

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Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer, NIH*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Benjamin Stratton, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

(b) (6) 16:29

Is availability of placebo going to be available, even if not used in scoring? Would inform the master protocol design.

(b) (6) 17:25

Good point. Not all commercially available agents have placebo to match ready.

(b) (6) 18:52

The distinction between biologics and syntheses is important.

(b) (6) 20:15

A suggestion would be to put a timeline cut off for availability - 12-18 months?

(b) (6) 23:34

Agree that availability for trial NOW is key but would think that availability for distribution could be something of a "tiebreaker."

(b) (6) 24:02

Agree with the tie breaker approach

(b) (6) 30:44

As a clinician in the "front lines", please know that "SOC" is fluid: yesterday's "best practice" is different today and will be different tomorrow.

(b) (6) 31:18

Agree.

(b) (6) 34:44

The Chinese "SOC" is one reason why clinical trial data from China even from RCTs is difficult to interpret. Even anticoagulation will be difficult to standardize.

(b) (6) 36:27

For IV drugs, we can use an unblinded pharmacist to prepare active and placebo. Logistically more complicated but doable.

(b) (6) 39:05

Perhaps we need to be able to track "wild-type" therapy--what is being done before a trial is initiated.

(b) (6) 39:24

we are collecting standard of care for COVID in the survey

(b) (6) **40:34**

Thanks, (b) (6)

(b) (6) **42:22**

This suggests that all agents will be testing a similar patient profile for efficacy - does this need to go into the choice of agent to be tested.

(b) (6) **42:58**

Yes, (b) (6), I think we will need to account for this in our first prioritization

(b) (6) **46:40**

For the choice of the agent, do we need to also take into account onset of action for each candidate. Will it be a confounding factor.

(b) (6) **54:21**

Thank you so much for your leadership.

High-Level Meeting Summary

The Agent Prioritization Subgroup of the TX-Clinical Working Group (APSG) discussed two revisions to the agent prioritization process. First, they agreed to adopt a collective review process that meets the highest standard for avoiding the appearance of any conflict of interest. Second, they agreed to several new steps to address the challenge of assessing candidate agents' potential mechanism of action (MOA) against COVID-19. With these revisions in place, the APSG will begin the triage phase of agent review by Monday, April 27, with the goal of recommending by May 1 a first wave of two to three candidate agents for immediate placement in the "repurposed" master protocol being developed by the Master Protocol Subgroup, assuming now that the trial will be ACTT3.

A summary of key discussion points follows.

Collective Assessment of Candidate Agents

Dr. Stacey Adam outlined a new collective assessment model to which the APSG agreed. Dr. Adam noted that pharmaceutical industry representatives will play an essential role in assessing candidate agents, and all ACTIV participants wish to avoid any appearance of a conflict of interest that may arise if members examine agents developed by their own firms. To achieve this important goal, the APSG will not rely on small panels constituted by area of expertise. The APSG discussed two alternate models: (1) assigning all APSG members to review all agents and (2) randomly assigning agents to multiple APSG members to triage first and then having the group score all the agents that pass triage independently.

For the triage stage, the APSG selected the latter approach, which they agreed would simultaneously protect against perceived conflicts of interest and manage the triage workload. At the subsequent review stage, all APSG members will score all candidate agents; scores will be averaged, with ties resolved by review panel consensus.

Assessing Mechanism of Action at Triage Stage

In its current form, the triage stage of the prioritization process puts each candidate agent on the Compound Inventory through an ordered series of five tests: (i) is the agent IND-enabled or FDA-approved; (ii) is the MOA relevant to COVID-19 and (iii) not already the subject of existing tests; (iv) is the agent already in robust clinical trials; and (v) is the drug suitable for populations prioritized by ACTIV. Only drugs that pass all tests move forward to review for prioritization.

The Challenge: Missing the Therapeutic Hypothesis

Participants noted that test (ii)—assessing a candidate agent's MOA *in relation to COVID-19*—may pose a significant challenge. The current ACTIV Compound Inventory identifies each agent's MOA but does not supply the rationale for supposing that the mechanism would specifically target SARS-CoV-2. In the absence of that information, APSG members may not be able to infer a therapeutic hypothesis. For example, participants were uncertain why tissue plasminogen activation (one MOA that appears on the list) would be expected to target SARS-

CoV-2; even agents with clearer potential rationales (such as inhibiting IL-6) may not have obvious connections to the natural history of the coronavirus.

Although participants were interested in gathering the missing information from the individuals and institutions that nominated the agents on the Compound Inventory, they recognized that this process cannot be completed before triage must begin. Instead, to avoid simply eliminating agents with unclear therapeutic hypotheses, the APSG will need to conduct research to surmise those hypotheses for assessment. However, APSG members also cannot feasibly conduct research on several hundred agents in the existing time frame.

The Solution: Random Overlapping Review of Agents with Shared MOAs

APSG members agreed on the need for a solution that manages the research workload while preserving the systematic prioritization process that is central to ACTIV (and that is of great interest to the clinical trial networks in ACTT). They agreed on a process to balance these goals.

- 1. Apply a screen to reduce the number of agents in the first wave.**

Dr. Adam will screen the master list for candidate agents with an FDA-approved indication to yield a reduced pool for initial triage. This screen is projected to decrease the pool from 250 agents to approximately 160 and potentially fewer than 100 if the group decides on strict regulatory approval status. Participants noted that the screen should take care to ensure that any gaps in spreadsheet data do not lead to the exclusion of qualified agents.

- 2. Sort remaining candidate agents by MOA to streamline the research process.**

Dr. Adam will sort the remaining candidate agents by MOA so that multiple MOAs' therapeutic rationales can be researched in parallel by distinct groups of APSG members, promoting the efficient use of the small window of time available for triage.

- 3. Randomly assign sorted agents in overlapping groups.**

Dr. Adam will randomly assign sorted agents to APSGs in overlapping groups of 16 (e.g., agents 1-16 may be assigned to APSG member 1; agents 8-24 to APSG member 2; etc.). This assignment will balance the need to divide MOA research with the need to ensure that no assessment is made by any single member of the APSG. Agents rejected by all reviewers will not proceed through the prioritization process; agents with discrepancies in reviewer opinion will be adjudicated; and all others will continue to the next stage.

Guidelines for Researching Therapeutic Rationales

The APSG agreed that its research may use a variety of approaches beyond traditional (but rapid) literature reviews. The ACTIV Compound Inventory often includes "Source Hyperlinks" that may provide information related to therapeutic rationale; literature reviews beyond this material may consider press releases as well as peer-reviewed publications; and members may take a bioinformatics approach to reviews, considering number as well as content of publications. Participants agreed that APSG members should document their findings so that they can be incorporated into subsequent ACTIV efforts.

Agents that Support Random Trial Assignments

Dr. Keith Gottesdiener described the Master Protocol APSG's interest in two to three agents that can support a completely equal randomization of trial participants, without contraindications that impose restrictions on enrollment. If the APSG can recommend agents that achieve this goal, he suggested that could be helpful even if those agents were not at the very top of the ultimate prioritization results.

Next Steps

Once the Compound Inventory is fully updated (with all publicly available information included and all duplicates removed), Dr. Adam will apply the screening and sorting process approved by the APSG and circulate random overlapping assignments to APSG members; any adjustments to the resulting list can be proposed and discussed by the APSG this weekend. Members will begin triage and report to Dr. Adam which agents they selected to continue in the prioritization process. Any discrepancies between reviewers will be discussed in the APSG's next meeting.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elliott Levy, MD, *SVP, Global Development, Amgen*

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STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Benjamin Stratton, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Ruxandra Draghia to Everyone: 02:08 PM

It would be great to flag directly in the table the compounds which are already in appropriate CT, which was our first "exclusion criterion".

From Mike Vincent to Everyone: 02:11 PM

Agree

From Timothy Buchman to Everyone: 02:13 PM

How many agents total are we going to be asked to score?

From Mike Vincent to Everyone: 02:13 PM

Supply and logistics might also allow a flag - for example, cell therapies might be excluded on that basis

From Stacey Adam to Everyone: 02:15 PM

We estimate about 200 agents for triaging in the first wave.

and then of those we think about 40 will need to be scored.

From Timothy Buchman to Everyone: 02:16 PM

Thank you for that overview.

From John Mellors to Everyone: 02:18 PM

Will probably need to a column in the spreadsheet for COI (Yes/No)

From Stacey Adam to Everyone: 02:18 PM

Hi John, yes, I was just going to cover direct COI

From Timothy Buchman to Everyone: 03:00 PM

Stacey, as always, thank you so much for your leadership.

From Ruxandra Draghia to Everyone: 03:01 PM

Yes!

High-Level Meeting Summary

The Agent Prioritization (AP) Subgroup of the TX-Clinical Working Group assessed potential alterations to a draft process to prioritize compounds for clinical trials. The AP Subgroup emphasized that the prioritization process must remain dynamic to ensure that recommendations anticipate and incorporate the most current data. At the level of the process's discrete stages, they agreed to: (1) adjust the precise definition and order of tests in the initial triage phase; (2) finalize category-sensitive criteria and a corresponding scoring system for candidate compounds in the review phase; and (3) proactively seek specific external sources of data about candidate compounds to aid in the prioritization. Triage will begin by April 24, and a first round of prioritized compounds will be identified by April 30.

The AP Subgroup also debated how to incorporate into the prioritization process candidate agents recommended by external groups. Participants agreed to vet those recommendations carefully, in part by soliciting and reviewing underlying data from the recommending groups.

A summary of key discussion points follows.

Iterative Prioritization Process

Dr. Stacey Adam outlined a four-step prioritization process developed through previous AP Subgroup meetings and conversations:

- 1) Organize candidate compounds into three categories: (a) antivirals, (b) host-targeted immune modulators, and (c) targeted support therapy (previously referred to as supportive/symptomatic therapy)
- 2) In small teams, conduct a rapid triage of candidate compounds in each category (teams may include members from other WGs as needed)
- 3) Review drugs that pass triage against specific prioritization criteria
- 4) Assess the top candidates from the review process against logistical benchmarks (e.g., availability)

Participants emphasized that the prioritization process must be iterative: while an initial round of priorities will be developed by April 30, subsequent drug data must be swiftly incorporated into successive rounds of prioritization to make the best possible recommendations. In addition, while antivirals and host-targeted immune modulators may seem most narrowly tailored to COVID-19, targeted support therapy is critical to addressing the virus's protean manifestations, which extend from respiratory distress to thrombosis, emboli, and renal failure.

Defining and Ordering Tests in the Triage Phase

The prioritization process begins with a triage that applies five screening tests to identify drugs available for Phase II or Phase III study. Drugs must pass all the tests to move to the next review phase; the AP Subgroup expects that at least 50% of candidate compounds will fail at this stage. The tests are: (i) is the drug IND-enabled and FDA-approved; (ii) is there clinical or preclinical evidence that the drug may treat COVID-19; (iii) is the drug already being tested in robust

clinical trials; (iv) is the mechanism of action relevant to COVID-19 and are other agents with the same MOA being tested; and (v) is the drug suitable for populations prioritized by ACTIV.

Participants clarified that “IND-enabled” (test i) is a capacious standard that does not require drugs to be FDA-approved. By contrast, they agreed that clinical and preclinical evidence (test ii) may be too vague a standard: many agents today are likely to have only weak clinical data derived from single-arm trials or compassionate use (one example is (b) (4) which was recently considered in just 8 patients with open-label drug experience). The AP Subgroup may consider altering the order of triage tests to ensure that this weakness does not eliminate virtually all compounds at the outset of the process.

Assessing and Acquiring Data in the Prioritization Phase

Following triage, candidate compounds will be prioritized according to several major criteria represented in a previously distributed spreadsheet: therapy type, clinical development stage, clinical evidence, MOA, and patient population. Some of these criteria duplicate triage tests but with a different purpose; they will be used to rank drugs on the list rather than build the list. Participants identified three elements that will facilitate prioritization work:

Category-Sensitive Criteria

Although participants broadly supported the criteria, they noted that they will require adaptation to each compound category: for instance, antivirals may exhibit widely divergent data in different assay conditions that will require careful assessment, while immune modulators may require attention to off-target effects and secondary infections. Participants noted that in assessing immune modulators, in particular, they may deliberately elect to choose compounds in different classes rather than use weak criteria to commit to one approach.

Accompanying Scoring System

Participants revisited their previous decision to bypass a scoring system in favor of expert gestalt review. Dr. Read noted that other prioritization processes have successfully aligned scoring and gestalt recommendations, and participants agreed to develop and test a scoring system. They observed, however, that no-go criteria must be differentiated from scores; for instance, safety concerns or an inability to obtain sufficient drug exposure via an IV solution would likely constitute no-go criteria that would override positive scores in other dimensions.

Compound Data

Participants discussed two potential sources of data that may aid the review process. Although they considered the Preclinical WG as a source of data, participants ultimately noted that WG is focused primarily on building resources to test compounds, not collecting compound data. However, they identified potential sources of real-world evidence for marketed products. A current effort called the COVID-19 Evidence Accelerator seeks to catalog these data, which may reveal serendipitous results (e.g., that patients taking drugs for other indications may show lower rates of COVID-19 hospitalization).

Lists of Compounds for Review

Participants noted that a wide variety of groups are assembling lists of candidate compounds to treat COVID-19, and some of these groups may have an interest in merging with ACTIV as efforts move forward. The master ACTIV list is the priority for this AP Subgroup, but members will review collected lists, as well, drawing on underlying data where available.

ACTIV List

The AP Subgroup will receive a master list of candidate compounds for ACTIV on Thursday or Friday of this week. The AP Subgroup will use the list to “pressure-test” and refine the draft prioritization process and simultaneously begin selecting compounds to move forward for testing.

External Lists

ACTIV has collected lists of compounds from three external efforts: the R&D COVID Consortium, ACTT2, and BIO. The WG will seek from external groups any underlying data that went into these lists’ development; participants noted that the main obstacle to this effort is likely to be a *lack* of data rather than an unwillingness to share it. Deloitte staff will assemble available data into the review spreadsheet developed by the AP Subgroup.

Next Steps

The AP Subgroup will submit additional recommendations regarding review criteria and accompanying scoring structure, both of which will be finalized by the end of this week. Members of triage teams will then begin to screen the ACTIV list of candidate compounds and report recommendations next week to the full AP Subgroup by Tuesday and then group will select final agents by Thursday, April 30.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomaterials Capital; Therapeutic Accelerator Lead, Gates Foundation*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Timothy Buchman to Everyone: 02:23 PM

The issue of a sufficient suitable patient population will be time-dependent.
Concur. And some of these data are appearing in high visibility journals despite quality issues.
Concur. This is another aspect of time-dependency. Incoming results and where the nation is in the pandemic wave(s)

This is important. Vanquishing the virus is complimentary to supporting the patient.

The immunotherapeutics may need additional information

Scope of cells where target/receptors are found.

From Timothy Buchman to Everyone: 02:38 PM

I wonder if we need two columns in the spreadsheet, one for mechanism of action and one that clearly outlines the rationale for believing that it will be effective in treatment.

From vincem10 to Everyone: 02:39 PM

Agree with that suggestion

From John Mellors to Everyone: 02:46 PM

Apologies, have to drop off

High-Level Meeting Summary

The Master Protocol (MP) Subgroup of the Therapeutics-Clinical Working Group (WG) discussed and agreed to revisions of the Repurposing and *De Novo* MP timelines. The Subgroup considered the use of independent writing teams for each protocol to maximize available time. It was agreed that critical design decisions must be made prior to dividing the group and writing the individual protocols. To facilitate these design decisions, participants discussed specific design elements for both Repurposed and *De Novo* MP development. The Subgroup agreed to prioritize design decisions for the Repurposed MP.

Protocol Creation Steps and Timeline

The Subgroup discussed the revised Repurposing MP and *De Novo* MP timelines. For both, two additional steps were included: (1) draft the Informed Consent Form (ICF) and (2) create the assignment algorithm. To accelerate the timeline for the Repurposing MP, time allocated to “drafting protocols” and “company review of the drafts” was reduced. Time was added to these steps for the *De Novo* MP timeline to ensure adequate preparation of the “gold standard” MP. Participants identified “selecting the optimal structure and statistical design” as a critical rate-limiting step for the *De Novo* MP and recommended applying any efficiencies of time (e.g., identification of repurposed drugs for the initial draft of the protocol) to developing the right structure and design. The Subgroup agreed on the revised Protocol Creation timelines, with initial work focusing on the Repurposing MP. Work on the *De Novo* MP will proceed after the Repurposing MP has made sufficient progress.

Strategic Approach to Protocol Creation

The Subgroup discussed establishing two independent writing teams to draft the Repurposed and *De Novo* protocols in parallel with periodic input from the entire Subgroup. Participants agreed these writing teams will not be formed until strategic elements for both the Repurposing and *De Novo* MPs are defined. The Subgroup also agreed to prioritize strategic elements for the Repurposing MP (i.e., ACTT3) first, while considering an overarching strategy that includes the *De Novo* MP. This timeline could allow for potential issues in ACTT3 to be addressed in the eventual *De Novo* MP.

Additional Considerations for Protocol Creation

Because the Repurposed MP will be built on ACTT, NIH will be its sponsor. NIH could sponsor the *De Novo* MP, as well, which would facilitate the IND process. If NIH sponsors the *De Novo* MP, contracting mechanisms through FNIH or other NIH flexibilities will be explored.

While the Repurposing MP may help to rapidly push a small number of existing drugs into clinical trials, the full range of therapeutic options cannot be tested in a matter of weeks. The Repurposed MP will allow time to develop the *De Novo* MP, but the *De Novo* MP must also progress quickly. The Subgroup emphasized that this fact should be communicated to NIH.

Design Considerations for *De Novo* Master Protocol

The Subgroup discussed two options for a phase II/III screening protocol: (1) identifying small phase II studies showing large effect size to move forward to a larger phase III study or (2) evaluating as many candidates as quickly as possible. Participants agreed there is a need to balance speed of amending the protocol with availability of candidates. Participants anticipated the *De Novo* MP may need to accommodate as many as a dozen novel monoclonal-based therapeutics, as well as additional candidates from biotech companies and new categories of existing drugs (e.g., anticoagulants) as more is discovered about the pathobiology of COVID-19. Participants questioned whether one protocol could serve two purposes: first screening a large number of candidates with low-likelihood and then developing robust data for those with promise. Member of the group suggested that an adaptive trial design could be used to rapidly screen therapies while allowing successful candidates to proceed to definitive examination. Candidates would then be introduced in rapid succession as other candidates are disqualified or deleted based on poor hazard ratios (HRs).

Further progress on the *De Novo* MP requires consideration of specific design elements: (1) primary and secondary endpoints; (2) length of follow-up; (3) screening and recruitment; and (4) additional statistical considerations. Participants also recommended pooling data from other trials, which may create efficiencies for screening candidates. It was strongly suggested that outpatient and inpatient populations be separated. The group agreed that separate populations could be recruited under two sister studies under one MP basic infrastructure.

Further discussion on the *De Novo* MP was tabled in order to focus on the Repurposed MP.

Design Considerations for Repurposed Master Protocol

The goal of the Repurposed MP is to determine the efficacy of currently available drugs in order to promote their use to standard of care (SOC). Recognizing the urgency for a short-term solution, the Subgroup agreed to use the ACTT trial network via protocol amendment for the Repurposed MP. The group offered two amendment options: (1) compare existing phase II candidates with modest effects for best efficacy; (2) identify small studies with big effects to progress to phase III. ACTT is currently designed to be a more confirmatory study. However, NIAID designed the Big Effects Trial (BET) to complement ACTT by enrolling several small arms to identify candidates with a large enough signal to feed into the ACTT pipeline. It may be worth considering design elements of both.

The Subgroup agreed that the Repurposed MP (i.e., ACTT3) should have multiple simultaneous investigation arms. Initial dosing will be defined, in most cases, by prior data on safety and amended by tolerability in the COVID inpatient population. ACTT3 must be nimbler than ACTT2 and able to handle multiple drugs simultaneously.

Additional design elements to consider include: (1) platform trial design; (2) evaluation of comparisons; (3) availability of matching placebos; (3) masking; (4) sharing control patients; (5) multiplicity issues; (6) randomization algorithm; (7) necessary adaptations (e.g., binding futility rule); and (9) analytic approach (i.e., frequentist or Bayesian).

Prioritization of Candidate Drugs

Because ACTT is a phase III design, initial prioritization of candidates should focus on those ready for a phase III trial. In addition, many early candidates may be drugs already approved by FDA for other indications. The Agent Prioritization Subgroup will prioritize a first round of agents by the end of April. The Subgroup recommends including three compounds in ACTT3, selected based first on prioritization order and then based on what is readily available.

Survey of Existing COVID-Related Clinical Trials

The Subgroup agreed some effort should be made to canvas for existing studies so that data already collected is not lost. One important consideration is defining the parameters for an adequate study from which data should be pulled. Dr. Stacey Adam and David Wholley explained FNIH is compiling a comprehensive list, including information from BioCentury and FasterCures databases. The first iteration will be ready for review this week.

Next Steps

Dr. Adam, along with the WG Co-Chairs and Subgroup Chair, will schedule 2 to 3 additional meetings this week to define strategic elements for the Repurposed MP. In addition, they will provide feedback to the Agent Prioritization Subgroup regarding the desire to begin by testing drugs that have prior FDA approval for other indications and that are already available in quantities sufficient for testing.

Appendix A: Participants List

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS)*

Joan Butterton, MD, *Associate Vice President, Infectious Disease Clinical Research, Merck*

Sylva Collins, PhD, *Director of Office of Biostatistics, CDER, FDA*

Judith Currier, MD, *Vice Chair, AIDS Clinical Trials Group (ACTG), UCLA*

Angelo DeClaro, MD, *Director (Acting) of Office of Biotechnology Products, CDER, FDA*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, NHLBI, NIH*

Keith Gottesdiener, MD, *President/CEO, Rhythm Pharmaceuticals (former)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC (TX-Clinical WG Master Protocol Subgroup Chair)*

Elliott Levy, MD, *Senior Vice President, Global Development, Amgen*

Amanda Peppercorn, MD, *Senior Medical Director, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Biostatistics Research Branch, NIAID, NIH*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Yuan-Li Shen, *Deputy Director (Acting), Division of Biometrics V, CDER, FDA*

Mike Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS FROM CTC WG

John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Peter Wung, *Deputy Director, Manufacturing Technologies, Sanofi*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Elizabeth Kim, *Senior Consultant, Deloitte*

David Wholley, M.Phil, *Senior VP of Research Partnerships, FNIH*

Kelly Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Peter Wung 01:03:06

Speaking of prioritization of drugs, will there be the possibility of testing combination of drugs as we will need to address that type of design as well in the writing of this master protocol?

Stacey Adam 01:03:33

We hope so Peter

Sam Bozzette 01:08:13

I am a bit confused - are we splitting into 2 groups soon?

Stacey Adam 01:08:57

Not yet. After we get through basics of repurposed

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group Working Group Meeting 7, Key Takeaways

Friday, April 24th, 2020

Action Items

Action Items		
	Information	POC
1	Update parameters that were decided from MPSG Meeting #6	Stacey Adam
2	Prepare ACTT3 Master Protocol first draft with language from ACTT2, leaving open the sections to be re-written for ACTT3	Stacey Adam/ Sarah Read
3	Continue discussions with the ACTT Investigators and arrange for them to come discuss the protocol with the MPSG	Sarah Read
4	Statistical subset of the group will meet Saturday to begin discussing and putting together the 2 recovery ratio options/power calculations	Lisa LaVange/FDA Statisticians/NIH Statisticians

Key Takeaways

- DECISIONS MADE FOR PROTOCOL STRUCTURE:
 - Adjust the reference that when we talk about what “time to recovery” that recovery actually means with respect to the top three scores in the ordinal scale.
 - Assume that we’re not stopping standard of care with a few exclusions to specific drugs outlined in ACTT2.
 - Therefore, it will be A+SOC vs. SOC, B+SOC vs. SOC, etc.
 - Stick to ACTT2 data collection and specimen sampling for the most part and keep the viral load collection optional.
 - TABLED to *De Novo*: Need stronger continuum (and corresponding statistics) in *de novo* protocol to pick up smaller things.
 - TABLED to *De Novo*: Modeling and simulations to arrive at the best adaptive design will be imperative for the *de novo* master protocol.
 - Stacey and Sarah to start creating the main protocol document for ACTT3 by porting over the language from ACTT2 that we are keeping but leaving open the sections that will need to be re-written.
 - Need more discussion on sample size and recovery ratio. We need 2 options to discuss. Statisticians will do multiple power calculations and come back to the larger group for a more informed discussion.

Recap of Previous Decisions by Stacey Adam

- For sample size, we would look at what is being done currently and it would be of similar size. We ended saying we’d talk about sample size today. And what kind of hazard ratio we’d power to.

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group

Working Group Meeting 7, Key Takeaways

Friday, April 24th, 2020

- Comment: Frequentist isn't "better suited" for what we are doing, but there's no good reason to change what's in ACTT unless we really want a good reason. Can consider Bayesian for next master protocol.
- Issues of standard of care variability (need to talk today)
- Add-on therapy (need to talk today)
- Would vote against using factorial designs, because of negative interactions that can bring down both interventions. We can't afford to risk negative interaction. Strong vote against factorial design.
- I'm curious about the idea that people who come into a 3+ arm trial just need to be eligible for 1 of the interventions as opposed to all of them.
 - Yes, we're doing that. If they are eligible for 2+ drugs, then we'll randomize between what they are eligible for.
- Suspect there's an enormous number of drugs that will have a small contra-indication and we will have very little restrictions on how we can use them.
- Will we randomize slightly larger portion to SOC than others so we can have a good power?
 - That probably isn't needed if we only have 2 or 3 compounds
 - Agree to see 3 drugs that can be used widely because we want early wins.
- Time to recovery will be classified as the patient moving into one of the top 3 scores on the ordinal scale.
 - I-SPY-COVID based out of UCSF moved to our primary endpoints
- We have to expect that people will look at the totality of the data and make decisions on all of those. Especially if secondary endpoints are bad for mortality.
 - People in the Seattle AIDS network were asking about time to mortality.
 - Secondary endpoint, we will be able to see what the progression is every day we measure it. I assume we need to measure it every day, or we will need to select what the last day will be.
- What about SOC in patients not randomized to SOC arm. The way we've written it, it appears it would not be allowed.
 - We haven't decided yet. The way I read ACTT2 people pretty much just stay on the care they come in with.
 - Second advantage of allowing and having a liberal policy with SOC means that changes to SOC would be expected to be reflected in all arms.
 - For completeness we should have drug A+SOC or something else.
 - What are we learning about what people are getting?
 - There's a lot of things people are using at this point.
 - There's a lot of other things in ACTT1 but not COVID treatments.

Discussion of SOC

- For this trial, if people said no hydroxychloroquine, I'm ok with that. We have to live with the fact that life is changing around us. If we're too prescriptive then we'll miss stuff.
- The concomitant from ACTT1 or 2 is probably approach we should adopt if it doesn't restrict enrollment. Is this a concern for the agents in the other group, that they can be put on the local SOC?

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group Working Group Meeting 7, Key Takeaways

Friday, April 24th, 2020

- We're probably not yet at a point where we can answer that question. The agent prioritization committee just received the first data pull.
- They have a who sheet of compounds broken into our categorization of drugs for wave 1, 2, 3, COVID-19 mAbs, and vaccines. Probably will end up with 400 total compounds across all waves and will probably end up with only 160 on the final list first wave list to be reviewed for triage. Probably 50-ish we'll score against criteria. Probably by Wednesday of next week. There is some thought to restricting our first review further to look at symptomatic/supportive therapies first.
- The agents that are prioritized initially will probably have limited contraindications or are at least widely combinable.
- DECISION: Will stay with local standard of care
- ACTT2 doesn't look that different from ACTT1. If so, local SOC trumps everything else. ACTT2 is different in that it doesn't allow biologics for lupus and others.
- Seems that the outcomes we're looking at will be in the record, why not just get it from the record?
 - Isn't it easier to just have these data from the study? The daily assessments are basically on/off ventilator, and in/out ICU. I don't think those assessments are that big of a deal. Obviously, someone in the hospital will. If it doesn't get entered, we won't be able to go back and get it.
 - There's a certain level of overhead associated with staffing to do assessments every day.
 - Yes, could be offsite, but we do need to decide if we need these every day. I would think which bucket though is easy for every day.
 - We will adjust daily care when we get our information.
 - Do we need viral load on days? The way the protocol is written is that those are encouraged but not absolutely required. Should be taken but just stored locally if possible. Don't want to exclude sites that might not be able to do those things
- Regarding PCR for COVID. Isn't the nasal swab more sensitive than oral? Why not go there, why stick at oral?
 - I think the principle is that we'll build on the work that's done by the ACTT1&2 teams and use the approaches they are under and are validating.
 - They do have a number of exploratory assessments, and that's not so much what we're about.
 - Here's things that are part of the study and here's things that are different. Some places will have some information and others won't. For viral load, don't need it for every person.
 - For ACTT3 we can have each site decide if they can do it
- Not sure we can do the last step of writing this without the agents

Writing Plan and Statistical Discussion

- Yes. Will need to change sample size because its written for the factorial and I guess the recovery ratio is the same. Could get 3-4 of favorite statisticians and just discuss what we want to write up.
- Have we made enough decisions that tomorrow's meeting means that we can just use as the statistician meeting?
- Same Recovery ratio is curious assumption...

Friday, April 24th, 2020

- It may not be the case that we'd hold all the interventions we'd be testing in this population. That's an interesting thought.
 - Next protocol you're right. This one, we need to consider but for this one. Do we hold them all to the same bar or do we different null hypotheses for each? We don't know how high the barrier is. What is the bar for recovery ratio?
 - Only looking in ACTT2, think it's 1.35.
 - It was based on 1.35, still resulted in 400 recoveries. So not sure we can afford that sample size.
- Are we doing ACTT2? Are we empowered to pick up something that isn't whopping, or do we want to make sure we get things that aren't whopping? Can we look at effect size, how would that work? Could go higher and look for something much lower than that in recovery rate and just don't want to miss something. In the factorial design, they have some ideas some things can double enrollment on that. Would need 400 recoveries in each of our comparisons, which is a lot of events.
- Do we know how this recovery ratio translates into some understandable clinical measure? Hard to know what 1.35 means? E.g. if we can shorten hospital stays by 25%, people want to know.
 - We could, if we assumed an exponential model, translate that to a difference in median days until they're recovered.
 - The only thing I would suggest is having some adaptive ability to adjust sample size as an iterative look. If something is <1.2 then might shut down, if 1.2-1.35 then might increase sample size so we don't miss something important.
 - Do we want something that isn't whopping but is important?
 - One thing to consider is it's not whopping but it is important. If you translate this the way, we usually do then the we're looking at a bad outcome then it corresponds to about a 25% reduction. It's not AS whopping as it sounds at first.
 - That's true but a 1.25 corresponds to a 20% reduction. At this phase in the epidemic, until we get a vaccine, if we can find a couple of drugs that reduce the risk of a bad outcome by 20% that's really good. More reduction is better, but yeah.
 - Agree but it will, of course need a bigger sample size.
 - Yes, but the difference is a philosophical one. Can test small number of drugs for smaller or more for higher. The latter should be one of the focuses of the *de novo* master protocol.
 - This is where the interim look and adaptive sample size in a grey zone is good. And a willingness to shut one compound down if it's not in the grey zone. We need to shut down and move quickly to something in the grey zone or better. I think we can both test more interventions and pick up some more moderate interventions if we're willing to be really brutal on things that aren't working.
 - Suggest falling back to what's happening in ACTT1&2. Fall back to that sample size in the "goldilocks" zone that those trials are using.
 - For *De Novo* would like to do some degree of modeling to identify the tradeoffs on sample size and study design.

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group

Working Group Meeting 7, Key Takeaways

Friday, April 24th, 2020

Chatbox

00:21:03 Michael Proschan: Sorry, I just got off another conference call.

00:21:59 sam bozzette: Do we really want daily assessments?

00:33:36 sam bozzette: when should we have gotten the ACTT2 protocol?

00:35:54 Stacey Adam: Sam, ACTT2 came about 2-3 meetings ago, but I can redistribute again today

00:42:52 Mike Vincent: ACTT2 excludes prior biologics, which seems to override the written SOC clause

00:44:38 sam bozzette: The way to do a project is to start doing the project

00:52:41 sam bozzette: RE effect size of interest: perhaps there is a gradient - we would be interested in a modest effect in hospitalized patients but a larger effect for outpatients or the exposed

00:53:33 Stacey Adam: Sam would that need to be considered here or just for the de novo since we would be looking at non-hospitalized patients

00:55:40 sam bozzette: yes - I would support looking for modest effects in hospitalized or certainly the intubated as the high risk of bad outcomes means that a smallish improved relative risk could still lead to a big risk difference

ACTIV, Therapeutics-Clinical Agent Prioritization Sub Group Working Group Meeting 2, Key Takeaways

Tuesday, April 21st, 2020

Action Items

Action Items		
	Information	POC
1	Agent Prioritization Subgroup Members who have not volunteered for the agent prioritization review process and wish to volunteer should inform Stacey ASAP	APSG Members
2	Update documents based on group feedback	Sarah Read, Erich Hughes, & Stacey Adam
3	Finalize list of Review Committee volunteers and consider creation of smaller groups within Review Committee	Sarah Read, Erich Hughes & Stacey Adam
4	Reach out to team that completed prioritization for ACTT to learn their thought process	Sarah Read
5	Circulate Frankfurt paper (https://www.researchsquare.com/article/rs-23951/v1)	Ruxandra Draghia-Akli & Stacey Adam
6	Share with Agent Prioritization Subgroup access to database of compounds	Stacey Adam

Key Takeaways

- Reviewed prioritization process, key criteria, initial triage process, draft criteria scoring, and sample lists of agents.
- Group aware that new information over the next several weeks may change prioritization assumptions and processes.
- Begin prioritizing agents by the end of this week, Friday, April 24th. ACTIV leadership wants to see list of first prioritized drugs by April 30th.

Review of Prioritization Process

- Review of clinical population prioritization and prioritization of agents in waves
- Walk through of the prioritization process for agents for ACTIV:
 - We have all the sources of candidate agents for prioritization. We're compiling into one spreadsheet.
 - We are grouping agents into 3 big classes – antivirals, host targeted immune modulators, and symptomatic/supportive therapy.
 - Once we have them divided into 3 groups, we will assemble small review teams to tackle each bucket.
 - First, each small review group will complete a simple triage of each agent.

Tuesday, April 21st, 2020

- Once the basic triage is done, the drugs that are still viable will be evaluated against review criteria (for which we sent out a basic numeric scoring sheet)
- Once those are reviewed against criteria with a scoring system, we will have our top candidates.
- Then, we assess supply, availability, and more logistical components associated with the agents.
- Suggestion by Co-Chair: instead of Mechanism of Action class, use “grouping of these agents into 3 categories”

Review of Initial Triage Flow

- Presentation
 - Is drug IND enabled/FDA approved: is it very ready to be used and likely already in clinic elsewhere?
 - Clinical/strong clinical evidence for the treatment of COVID?
 - If so, are there already robust clinical trials ongoing?
 - Then talk about Mechanism of Action and how relevant it is relevant to SARS-CoV2, and if already agents in class being tested
 - Then, is it suitable for our patient population? We have these set up in yes/no rubrics through each of questions.
 - The hope is that this fast triage would eliminate good percentage of drugs, 50% or better, and give each smaller team more manageable number to work with.
- Questions from WG members
 - A lot of these agents will have clinical data.
 - Need to think about criteria very carefully – a lot of these are single arm, and some of the data is not worth much.
 - A really good clinical model would take over poorly done clinical experience that’s not very convincing.
 - Parts of flow chart that should really be left to expert panel for review:
 - What passes for clinical/strong preclinical evidence
 - Suggestion to make triage flow dynamic. We’ll get information along the way that will change our assumptions about what works and does not work.
 - Group suggested switching the ordering of MoA and preclinical treatment boxes.
 - Clarify meaning of IND enabled (all IND enabling studies are done; IND may not be submitted. Enabled means not necessarily granted.)
- Importance of considering the protean manifestations of COVID-19. Supportive therapies are really important. People are dying of a variety of complications: thrombosis, emboli, renal failure – it is beyond the lungs. We need to pay attention to those categories as it may be lifesaving.

Tuesday, April 21st, 2020

Criteria Excel Spreadsheet

- This level of criteria assessment would follow the initial triage flow.
- Additional categories or changes needed considering immunotherapeutics?
- Importance of considering different assay conditions
 - ACTIV Preclinical WG is mainly focused on compiling resources for testing preclinically.
 - May find preclinical studies, but preclinical models are largely not good. There is not a lot of preclinical data.
- Group asked if there was a way to collect Real World Evidence for use in evaluation. There is a group attempting to collect this data in the COVID evidence accelerator discussion that was launched today: <https://www.focr.org/covid19>

Key Criteria Scoring (post initial triage)

- Suggesting scoring mechanism to the WG. May help to arrive at prioritization with some quantitative component. This will take additional testing and modification.
- Scoring makes sense, but WG members not sure if the numbers are intended to be proportional.
- Need to revise the weighting of scoring
- Need to define what are “no go” criteria, for example certain safety profiles and availability.

Review Committee Determination

- Still finalizing list of volunteers
- How do we want to further subdivide the smaller Review Committee groups?
- Make sure that smaller groups provide recap to larger Agent Prioritization WG

Agents Selected for ACCORD review, R&D Consortium 1st wave, and Drugs assessed for ACTT2

- Agents selected by R&D consortium
 - Each of the companies that were part of the Consortium went through their own pipelines, did their own evaluations, and each brought forward to 3-5 candidates. The R&D Consortium then top candidates and came up with this list.
 - Background on R&D Consortium: 13 heads of major R&D companies that formed R&D COVID consortium. Keith Gottesdiener and Elliott Levy are part of this Consortium. There is a potential for R&D Consortium and ACTIV to synergize efforts and eventually merge.
- All of these lists and data are being funneled into our agent selection process.
- The information will be inserted into a database that Deloitte is working on. The database will be populated for the WG, and items will be searchable by agent, generic name.
 - Request from Keith Gottesdiener packet of information providing candidate selection rationale by R&D Consortium

ACTIV, Therapeutics-Clinical Agent Prioritization Sub Group Working Group Meeting 2, Key Takeaways

Tuesday, April 21st, 2020

- Reach out to team that did prioritization for ACTT to see if their thought process would be helpful for ACTIV (Sarah Read)
- When looking at short list of agents, important to prioritize in a rational way and not just because a company has a pet project or likes a particular compound (scoring criteria should help with this).
- Meeting with team from Bio:
 - They did a review of all of their member company pipelines and focused on antivirals.
 - They shared with us a document about their process.
 - Antivirals – results from ongoing studies may come in next 2-3 weeks. We can prioritize on available data, but we will probably have to go through quality control when that data is published.

Meeting Recap

- WG needs to finalize: criteria, scoring (including go/no go), triage process
- Begin prioritizing agents by end of this week Friday, 4/24
- Francis Collins would like to see first prioritized drugs by April 30th
- If additional expertise/reviewers needed, we can onboard additional experts.
- By the end of the week next week, we need candidates to go into the first “repurposing” Master Protocol. These should be agents that are more developed.
- Importance of understanding what papers are in review, trials completed, etc., for greater situational awareness.

Chatbox

From Timothy Buchman to Everyone: 02:22 PM

The issue of a sufficient suitable patient population will be time-dependent.
Concur. And some of these data are appearing in high visibility journals despite quality issues.
Concur. This is another aspect of time-dependency. Incoming results and where the nation is in the pandemic wave(s)

This is important. Vanquishing the virus is complimentary to supporting the patient.

The immunotherapeutics may need additional information

Scope of cells where target/receptors are found.

From Timothy Buchman to Everyone: 02:38 PM

I wonder if we need two columns in the spreadsheet, one for mechanism of action and one that clearly outlines the rationale for believing that it will be effective in treatment.

From vincem10 to Everyone: 02:39 PM

Agree with that suggestion

From John Mellors to Everyone: 02:46 PM

ACTIV, Therapeutics-Clinical Agent Prioritization Sub Group
Working Group Meeting 2, Key Takeaways

Tuesday, April 21st, 2020

Apologies, have to drop off

High-Level Meeting Summary

The Master Protocol (MP) Subgroup of the Therapeutics-Clinical Working Group (WG) discussed its envisioned ‘hybrid approach’ to simultaneously developing a Drug Repurposing MP (fastest timeline) and a *De Novo* (‘Gold Standard’) MP, including proposed assumptions and estimated timelines for both (full breakdown of assumptions development steps in meeting slide deck).

The Drug Repurposing MP should be finalized rapidly, ideally within fewer than 30 days, with the *De Novo* MP timeline slightly extended to ensure that it includes all desired parameters, generates high-quality data, facilitates rapid evaluation/replacement of candidate therapeutics, and functions optimally under a central Institutional Review Board (IRB) and Data Safety Monitoring Committee (DSMC).

Industry representatives agreed to one round of company review of the draft MPs to accelerate both MP development timelines. To accelerate initiation of trials, the *De Novo* MP may simplify Phase 2 data collection protocols, while allowing for more complex data collection during Phase 3 to ease initial site burden.

Participants also emphasized that a key facet of ACTIV’s overall remit is to “think big” and set ambitious goals. For example, MP Subgroup members have suggested aiming to establish 500 to 1,000 sites to run trials under its *De Novo* MP, in part to test newly developed antivirals and monoclonal antibodies that may emerge in the coming months. This bold mentality motivates the aggressive timelines proposed by this Subgroup, which should be explicitly conveyed to the ACTIV Leadership Group.

Participants cautioned that for both Drug Repurposing and *De Novo* MP development, the 14-day timeline estimate for creation of a technical database structure may be overly ambitious, particularly given the potential complexity of adaptive trial design. One assumption underlying a 14-day timeline is that ACTIV will save time by using ACTT case report forms (CRFs).

The Drug Repurposing Master Protocol

The Subgroup reviewed proposed assumptions and timelines (31 to 47 days) for establishing its Drug Repurposing MP (by amending the ACTT2 protocol) to rapidly begin testing of previously approved compounds selected by the Agent Prioritization Committee (APC) for Phase III testing. Despite concerns that ACTT2 will require substantial revisions, participants agreed to develop an ACTT3 MP to test the top two to four compounds advanced by the APC, which will enable rapid initial testing using the 75 existing ACTT2 sites while the *De Novo* MP is in development.

The *De Novo* ‘Gold Standard’ Master Protocol

Estimated Timeline Discussion

Although the Subgroup recommended extending the estimated timeline for developing the *De Novo* MP (initially set at 42 to 61 days) to ensure that all parameters are designed for optimal quality and efficiency, it also stressed the need to launch trials quickly once the MP is finalized.

The Subgroup therefore agreed to create a central IRB and DSMC for all sites conducting trials under the *De Novo* MP, and one contract structure for all companies and clinical trial networks.

To accelerate launch of first wave *De Novo* MP trials, Subgroup members suggested designing two separate protocols, conducted 1 to 2 months apart, for (1) hospitalized patients and (2) pre-hospitalized patients. They also suggested omitting complex procedures, such as response adaptive randomization, in favor of covariate adaptive randomization. The initial *De Novo* MP will focus only on inpatients to streamline trials; ambulatory care and prophylaxis therapeutics will be targeted by second or third wave trials under a different MP.

The timeline for developing a *De Novo* MP should also reflect drug supply timelines.

***De Novo* Trial Network**

The Clinical Trial Capacity WG is conducting surveys of clinical sites to compile an inventory of trial capacity that will then allow it to match networks to the parameters specified by the *De Novo* MP. The network of sites established to conduct trials under the *De Novo* MP must be capable of testing at least four therapeutics simultaneously and of rapidly identifying and replacing failed compounds. Some compounds may also be tested by subsets of sites within the network.

Leveraging Existing Master Protocols

Participants agreed to use existing MPs as templates and to harmonize endpoints with existing trials wherever possible, while also considering the FDA guidance on endpoints for COVID-19 therapeutics (to be released this week). Two goals were highlighted: (1) selecting endpoints that generate a clear, simple message that will resonate with regulators and clinicians, and (2) simplifying existing MP designs wherever possible to improve efficiency.

Next Steps

Dr. Stacey Adam, along with the WG Co-Chairs and Subgroup Chair, will shorten the timeline for developing the Drug Repurposing MP and extend the timeline for developing a *De Novo* MP. They will also develop a unified contracting mechanism for clinical trial networks and contributing companies to facilitate rapid onboarding of new sites and organizations into the ACTIV clinical trials infrastructure. Subgroup members will also review other existing MPs and prepare a list of desired elements for the *De Novo* MP to discuss during tomorrow's meeting.

Appendix A: Participants List

SUBGROUP MEMBERS

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS)*

Joan Butters, MD, *Associate Vice President, Infectious Disease Clinical Research, Merck*

Sylvia Collins, PhD, *Director of Office of Biostatistics, CDER, FDA*

Judith Currier, MD, *Vice Chair, AIDS Clinical Trials Group (ACTG), UCLA*

Angelo DeClaro, MD, *Director (Acting) of Office of Biotechnology Products, CDER, FDA*

Mark Eisner, MD, MPH, *Senior Vice President and Global Head of Immunology, Infectious Disease and Ophthalmology Clinical Development, Genentech*

Keith Gottesdiener, MD, *President/CEO, Rhythm Pharmaceuticals (former)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC (TX-Clinical WG Master Protocol Subgroup Chair)*

Elliott Levy, MD, *Senior Vice President, Global Development, Amgen*

Sandeep Menon, PhD, *Senior Vice President and Head of Early Clinical Development, Pfizer*

Amanda Peppercorn, MD, *Senior Medical Director, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Biostatistics Research Branch, NIAID, NIH*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Yuan-Li Shen, Deputy Director (Acting), Division of Biometrics V, CDER, FDA

Mike Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS FROM CTC WG

John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Peter Wung, Deputy Director, Manufacturing Technologies, Sanofi

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, M.Phil, *Senior VP of Research Partnerships, FNIH*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Sam Bozzette 29:11

are we thinking big enough with respect to the scope of the trial per se?

default user avatar

Peter Wung 42:37

Will the ICF timelines be concurrent to this?

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Menons09 43:11

Agree with the comment on IVRS. We need to ensure drug supply is aligned too with the IVRS.

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Menons09 48:16

Do we need to get any assay's ready?

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menons09 56:49

When is the FDA guidance for endpoints going to be released? Need to align with regulators

ACTIV, Cross-Trial Operations Meeting

Thursday, January 21st, 2021

Action Items

Action Items		
	Information	Owner(s)
1.	If you would like to receive a morning update from Deydre Teyhen that consolidates updates relevant to therapeutics from about 10-15 different emails, please send her your email and she will be glad to add you to the list.	All
2.	Send one email to Peter Kim and another to Rachel Harrigan with question regarding government indemnity.	Jane Atkinson
3.	Forward Jane Atkinson's inquiry to Judy Currier and A.CTG contracts team	Peter Kim
4.	Run Jane Atkinson's inquiry by the ACTIV-3 Team to determine how they have gotten around it.	Rachel Harrigan
5.	Gut-check the attached slides (to the meeting invite) from the ABPC to make sure none of the information is glaringly incorrect.	All

Meeting Summary

- ACTIV-2, V3.0 and ACTIV-3, V3.0 have received Safe-to-Proceed.
- Slight delay of ACTIV-4c → launch date looking to be mid-February
- Introduction of ACTIV Biospecimen Prioritization Committee (ABPC) structure and process prior to presenting to the broader team next Friday.
- Lessons learned from the IQ Solutions Listening Sessions will be continued during the next meeting.

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Updates
- Biospecimen Prioritization Committee Structure and Process
- IQ Solutions Listening Sessions – Lessons Learned
- Meeting Recap

ACTIV Trial Status Updates (Stacey Adam)

- ACTIV-1: 28 sites open; (b) (4) as of 01/20
 - Team is reviewing FDA comments on statistical analysis plan
 - Evaluating and selecting participating sites; 23 sites selected in Latin America
 - Jane Atkinson: Some California universities were wanting more comprehensive indemnification from the drug companies (these are institutions that are also participating in ACTIV-2 and ACTIV-3) – Peter Kim can forward this question to Judy Currier and ACTG contracting team; the federal government is not allowed to indemnify anyone or anything
- ACTIV-2: 95 sites open; (b) (4) as of 01/20
 - (b) (4) open-label study and (b) (4)

ACTIV, Cross-Trial Operations Meeting

Thursday, January 21st, 2021

- (b) (4) on 01/05; (b) (4) closed after 01/15, now recruiting ONLY to (b) (4)
- Version 3.0 received Safe-to-Proceed
- ACTIV-3: 34 sites open; (b) (4) as of 01/21
 - Version 3.0 received Safe-to-Proceed
 - ACTIV-3b/ TESICO protocol reviewed by NIAID Regulatory Group and submitted to the FDA on Monday, 01/18
 - ACTIV-2 and ACTIV-3 have been approved for the VA
- ACTIV-4:
 - (4a) Hospitalized: 58 sites open; (b) (4) as of 01/20
 - Partnered off with a couple of additional trials – ATTACK trial and REMAP CAP trial
 - (4b) Pre-hospitalized: 11 sites open; (b) (4) as of 01/20
 - Still awaiting final signature on contract with CVS; allowing CVS to become sites for them and expanding enrollment
 - Post-hospitalized received first drug shipment on 01/05
 - Slight delay; looking at a mid-February launch date
 - *Hospitalized and pre-hospitalized cohorts launched on Sep.17; post-hospitalized cohort targeting launch in late January*
- ACTIV-5 (Big Effect Trial): 9 sites open (goal = 40 sites); (b) (4) as of 01/13
 - Identifying other sites; 16 more patients in process of enrollment
 - Assessing/ prioritizing additional investigational agents
- Convalescent Plasma Trials – enrolling well
 - CONTAIN COVID-19
 - 17 sites; (b) (4) as of 01/20 (target = 1,000 patients)
 - Next DSMB meeting 01/22 to review data from the first ~700 patients
 - Adding up to 13 more sites; UT Rio Grande Valley and 2 Milwaukee hospitals expected to enroll first patients by 01/22
 - PassItONII
 - 22 sites; (b) (4) as of 01/20
 - Next DSMB meeting on 01/26 to review data from first 450 patients
 - Adding up to 11 more sites; UChicago and UArkansas activated on 01/08
 - Rationale and design manuscript in preparation
 - C3PO
 - 51 sites; (b) (4) as of 01/21
 - Working with 65 sites
 - DSMB met on Tuesday, 01/19 to review sample size estimate based on total event rate from 300 patients (no outcome yet); next DSMB meeting is planned for 01/29 (we will find out then if there need to be any corrections for sample size)
 - Perhaps need to start collating information and have a template for the individuals on the operations side to look at and reference

ACTIV, Cross-Trial Operations Meeting

Thursday, January 21st, 2021

Biospecimen Prioritization Committee Structure and Process

(Stacey Adam)

- Not a central bio repository as it stands now (although there has been some desire expressed around that)
- Objective: The ACTIV Biospecimen Prioritization Committee (ABPC) is intended to be a committee that would establish a unified cross-active effort to evaluate, prioritize, and approve secondary research requests for accessing biospecimen collected from the ACTIV trials.
- The ABPC will be working to create a list of priorities then they would be a committee that would evaluate against those priorities if they did find values in any of the proposals that came in, then 'work with each tea to allocate the samples from their trials and wherever they are currently being housed.
- Scope - ABPC responsible for:
 - definition and revision of scientific and clinical evaluation guidelines for biospecimen requests
 - Collection, evaluation, prioritization, and approval/ rejection of biospecimen requests
 - Communication of review decisions
- When evaluation biospecimen requests, the ABPC considers the following: 1. agreement of use (all parameters of use have been agreed by the requesting investigator; 2. research focus (focus and aims should address top-priority, unanswered questions and are supported by strong evidence); 3. experiment design (study is well-designed and carefully planned; biospecimen are appropriate to address intended questions, intended assays are well-established and well-accepted and quantities of biospecimen are reasonable for the assays); 4. Investigator/ institution (adequate funding, credible lead investigator, and institution is well-equipped and well-resourced)
- ABPC will be comprised of:
 - Oversight committee – Trial Sponsors (NIAID, NCATS, NHLBI, and others)
 - Review Committee – Active Trial Team reps, 2-3 Academic experts, and 2-3 Industry reps
 - Project Management – one or multiple NIH ICs
- ABPC will adopt a streamlined process to ensure consistent, transparent, and timely evaluations of biospecimen requests.
 - External investigators submit a request → offline review → group adjudication → decision sign-off
- Please see the two slides that were circulated with the meeting invite. Collected ICFs and protocols and looked for what specimens are being collected and what each trial's informed consent allows – have the ICFs and trial collections been accurately characterized? Feel free to share with Trial Teams.

IQ Solutions Listening Sessions – Lessons Learned

(Linda Silverstein, IQ Solutions)

- Recruitment Summary – Challenges:
 - Inpatient studies with very sick patients – difficult to obtain consent
 - Some consents take up to two hours (if there are multiple treatments)

ACTIV, Cross-Trial Operations Meeting

Thursday, January 21st, 2021

- Some sites are doing multiple studies and down staff
- Most COVID patients are men; less women
- Some sites are still being activated
- Less opportunity to educate healthcare professionals (less congregation in cafeterias and grand rounds)
- Difficulty in recruiting patients to mAb trials when mAb treatment is available
- Recruitment Summary – Opportunities:
 - Additional funds from OWS to enhance outreach
 - Will advertising to the public create awareness for inpatient studies?
 - Additional materials for HCPs
 - Need to expand campaign on donating and receiving blood plasma
 - Leverage ACTIV-4's engagement of CVS Health to help ID patients
 - Leverage PassItOn's (600) community stakeholders
 - Use of infographics and flip books to simplify the informed consent process
 - Make more videos of successful sites to talk about their approach and research
- Rachel Harrigan: the ACTIV-3 team has found the flip-books extremely useful especially with a consent process getting more complicated with having two products in the study at the same time and having to explain a two to one randomization to the patients with a three step consent process
- Rachel Harrigan: How does the strategy come together across a variety of inpatient studies across the COVID-19 ecosystem (e.g., Duke doing a number of different inpatient studies; revealed this week that they will target screening 25 subjects/day for a variety of 3 or 4 different inpatient studies)?
 - This conversation will be continued during the next meeting so as not to rush this important discussion.

CHAT

- Deydre Teyhen07:39: I will need to drop off at 0925.
- Stacey Adam08:09: Thanks, Deydre, understood.
- Kevin Bugin11:10: NSTC is the science council
- Linda13:01: Yes please! (b) (6)
- Alan Embry13:38: Thank you Deydre. That would be great!
- Kevin Bugin17:45: If individuals are participating in clinical trials and they are injured or die after being administered or using a covered countermeasure, then they may file a claim and be eligible for compensation from the Countermeasures Injury Compensation Program.
- Kevin Bugin17:55: Through HRSA
- Kevin Bugin18:44: <https://www.hrsa.gov/cicp>
- Deydre Teyhen34:21: Sorry - I have to drop. Thank you! You all are brilliant and 10 steps ahead of me!
- Sarah Dunsmore35:45: Thanks Deydre! Valid points of discussion - thanks for raising!
- Sarah Dunsmore47:26: What is the anticipated lifetime/timeframe of the ACTIV Biospecimen Prioritization Committee?
- Sarah Dunsmore57:46: Convalescent plasma trials also have to deal with an EUA
- Andrea Lerner01:05:46: apologies I have to drop

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics elevated for its consideration, including the processes by which the Agent Selection Committee (ASC) and Agent Prioritization Committee (APC) recommend (b) (5)

Dr. (b) (6) also discussed with the TOC logistics relating to the presentation of efforts on new SARS-CoV-2 variants.

Trial Accrual and Status Updates

The TOC received updates on ACTIV-2 and ACTIV-3 accrual and onboarding of new agents.

ACTIV-2

ACTIV-2 has activated 94 sites and (b) (4). The ACTIV-2 team anticipates FDA (b) (5) on January 19, 2021, which will include the addition of four new agents: (b) (4). Trial enrollment is strong, and demographics are well-distributed. In addition, ACTIV-2 is moving ahead with plans for co-enrollment with a vaccine trial. The ACTIV-2 trial team expressed minor concerns about the potential for a decline in enrollment after ACTIV-2 shifts from open enrollment on the (b) (4) drug to blinded enrollment on the (b) (4) on January 15. These (b) (5)

Discussion

TOC members inquired whether the ACTIV trial teams had any insight into the nationwide lack of enrollment to mAbs that have EUAs. Trial team members felt that the main issue is (b) (5) (e.g., nurses) at hospital sites. Dr. (b) (6) agreed that the logistics of providing agents approved for emergency use to hospitals that are already over-burdened is not effective. (b) (6) advised the TOC that Operation Warp Speed (OWS) plans to launch direct ordering, which will permit the procurement and infusion of agents under EUA by various types of skilled nursing facilities, including urgent care, home infusion services, dialysis centers, specialized ambulance services, and nursing home pharmacies.

ACTIV-2 data from the (b) (4) phase II study have not yet been unblinded. Dr. (b) (6) that the first delay was in reaching agreement on when data would be locked for analysis (i.e., what constituted the 28-day follow-up period). (b) (4) originally proposed a data lock by March 3 but, based on recent discussions, has revised that timeline to mid-February. Two factors remain: (1) who will complete the analysis and (2) how fast the analysis can be completed. The determination of who will analyze the data will be based on who will use the data: if (b) (4) will use the data for FDA submission, then (b) (4) will perform the data analysis. The ACTIV-2 team is awaiting a response from (b) (4) on this point. Dr. (b) (6) reiterated a previous query about whether it would be possible to release top-line data first, followed by full data for an FDA submission, noting that doctors would be primarily interested in any safety, virology, and

clinical data from the phase II study. Dr. (b) (6) suggested emphasizing to (b) (4) that ACTIV-2 does not need a regulatory package from these data.

ACTIV-3

ACTIV-3 has activated 30 sites and (b) (4) in Version 2 of its protocol. Demographics also are well-distributed for this trial. ACTIV-3 had its first Version 2 post-enrollment DSMB meeting on January 4, 2021, following several infusion-related reactions at one study site. The DSMB concluded it was safe to proceed but requested assessment of whether these events fulfill the case definition for anaphylaxis. A classification was submitted to the DSMB yesterday together with a memo from ACTIV leadership asking that the DSMB evaluate the accumulation of these events.

ACTIV-3 is awaiting FDA approval for Version 3, which will add the (b) (4). Several new sites are anticipated to register now that the holidays are over, and ACTIV-3 is on track to enroll (b) (4) by early February, at which point a futility assessment will be conducted, and the ACTIV-3 team has also requested a formal DSMB assessment on January 25. In addition, ACTIV-3 is working on launching ACTIV-3B, a factorial study of (b) (4) (b) (4), (b) (5) in patients with acute respiratory distress syndrome (ARDS). Currently the team is preparing for their pre-IND meeting for (b) (4).

Discussion

ACTIV-3 has received conflicting feedback on protocol Version 2 from (b) (4). Some (b) (4) have expressed concerns that there are insufficient phase I data for (b) (4) agent to move on to phase II studies and have requested a longer follow-up (i.e., longer than 90 days). A provision in the phase II protocol allows follow-up out to 18 months, but extended follow-up poses additional challenges. Dr. (b) (6) noted the 90-day follow-up of (b) (4) drug will be complete in 10 days and may shed light on what data could be gained from a longer follow-up as well as on ACTIV-3's novel *sustained recovery* outcome. Regarding Version 3, the ACTIV-3 team has resubmitted a streamlined informed consent form that removes agent-specific drug information sheets to avoid the need for additional signatures, which has posed challenges in the consent process. Site training for Version 3 will begin early next week. Sites registered to Version 3 of the protocol will randomize patients to receive one of three mAbs—from (b) (4). For those foreign sites that do not feel (b) (4) phase I data are sufficient to support a phase II trial, patients will likely be randomized to one of three arms: (b) (4).

Dr. (b) (6) recognized the lack of harmonization between different regulatory bodies as an issue within the clinical trial ecosystem that has been highlighted by the response to COVID-19 and that should be improved upon for the future. (b) (6) offered to raise this issue during her regular call with (b) (4). Dr. (b) (6) noted that FDA has also been meeting regularly with the European Medicines Agency (EMA) and requested that he be notified if the ACTIV trial teams encounter any similar issues with EMA. Dr. (b) (6) suggested recognizing countries that have handled this challenge well (e.g., Peru) as examples for other countries' consideration. ACTIV trial team leads emphasized that the lack of regulatory

harmonization is also a domestic problem, noting difficulties with the VA launching ACTIV-2/-3 trials due to delays with their local IRB. Dr. (b) (6) offered to contact (b) (4) to discuss the requirement for local IRB review for COVID-19 agents already reviewed by a central IRB.

Topics for Discussion

The TOC discussed topics escalated for its consideration.

Processes for Agent Selection and Prioritization

TOC members discussed how decisions are made about what agents are studied in ACTIV-2/-3 trials and with what degree of priority. They briefly reviewed the scoring criteria for different classes of agents, noting the scoring systems were iteratively refined between the initial prioritization of existing (repurposed) agents and subsequent rounds of agent prioritization, with consideration of additional data from ongoing clinical trials as well as increased understanding of the pathogenesis of COVID-19. In addition, the ACTIV-3 master protocol contains an appendix defining standard of care (SOC) as a background treatment. NIH treatment guidelines for COVID-19 are used to determine when to incorporate new agents into this background treatment.

Recommendations for agent prioritization come from two groups: the APC and the ASC. The APC prioritizes antivirals, immune modulators, and symptomatic/supportive therapies across all seven ACTIV trials, while the ASC prioritizes mAbs (and related agents) specifically for ACTIV-2/-3 trials, using a related set of scoring criteria specific for this class of agents. APC and ASC scores act as a starting point for prioritization discussions, with many agents (currently over 20) deferred pending additional information from sponsors and/or readouts from phase I clinical trials. Additional factors considered in agent prioritization include the capacity of ACTIV clinical trials and whether agents are being evaluated in other ongoing robust clinical trials.

Incorporation of New Findings from Other Ongoing Studies

Among the criteria used to prioritize agents is whether they are under investigation elsewhere. For agents evaluated in other trials, there is now a diverse and sometimes contradictory set of clinical trial results from a series of underpowered clinical endpoint studies that are often performed in non-traditional settings and for which little is known about potential selection bias in reported outcomes. Despite these potential shortfalls, the studies can provide strong talking points for advocates. For example, REMAP-CAP reported positive outcomes from a randomized trial of the (b) (4) in critically ill COVID-19 patients; however, only (b) (4), and the study controls were unclear. Similar issues have been observed for trials evaluating ivermectin and convalescent plasma.

Dr. (b) (4) offered two recommendations relative to agent prioritization: (1) maintain an awareness of the landscape to ensure ACTIV moves forward with the highest priority candidates, and (2) follow up on deferred agents and candidate agents that were triaged based on the expectation that they would be carried forward by other trials.

Coordination across ACTIV Trials

It is not always clear which ACTIV trial is the best fit for a particular agent, and some candidate agents may fit well in more than one protocol. In these cases, ACTIV trial team leads are engaged in a joint conversation to determine where an agent can most efficiently enter a trial. (b) (4), for example, was a departure from the agents typically included in ACTIV-3. This agent was offered to ACTIV-1 first, with other immune modulators, but ACTIV-1 was unable to onboard another agent at that time. Often (b) (6) from ACTT is included in these cross-trial conversations to provide another potential avenue for clinical trials in hospitalized patients.

ACTIV Clinical Trial Capacity

Dr. (b) (6) noted the length of time it has taken ACTIV-2 to open 94 sites. This time was due in part to site activation but is also a consequence of the absolute number of sites available for trials. A mismatch between trial capacity and the number of candidate agents may risk jeopardizing studies for any single agent due to insufficient enrollment to power statistically meaningful conclusions.

Creating a Novel, Pragmatic Clinical Trial

To properly evaluate oral drugs that have reported some efficacy against COVID-19 in small, randomized trials or case series (e.g., (b) (4)), TOC members discussed the possibility of conducting a “low-touch” pragmatic trial (e.g., similar to the (b) (4) trial) in ambulatory non-hospitalized patients. Such a protocol would not evaluate long-term follow-up or exploratory endpoints, instead focusing on a single clinical outcome (e.g., whether treatment significantly reduces hospitalization). TOC members inquired whether such a pragmatic trial would be sufficiently robust for the NIH treatment guidelines panel to recommend treatment should the effect be positive. Dr. (b) (6) indicated the committee would likely be receptive, noting the (b) (4) trial has a similar study design. Dr. (b) (6) offered to advocate for funding to support this effort. TOC members offered suggestions for potential trial networks to conduct this novel pragmatic trial:

ACTIV (i.e., ACTIV-6) – The ACTIV-2 team requested feedback from the NIH treatment guidelines panel regarding the most pressing questions for a potential ACTIV-6 to answer. Dr. (b) (6) recommended discussing the potential for a pragmatic trial with the TX-Clinical WG at their meeting on Thursday.

(b) (4), (b) (5) – Dr. (b) (6) highlighted possible alignment of a pragmatic trial for repurposed oral drugs with (b) (4), (b) (5)'s efforts, because these oral agents are often widely available as generics. Dr. (b) (4), (b) (5) offered to facilitate conversations with (b) (4), (b) (5) regarding a potential collaborative ACTIV (b) (4), (b) (5) effort, noting that a (b) (4), (b) (5) representative would likely attend the TX-Clinical WG meeting.

(b) (4), (b) (5) To gauge the interest and ability of (b) (4), (b) (5) to contribute resources to a pragmatic trial, Dr. (b) (6) recommended engaging (b) (6) at NHLBI and (b) (6) at NINDS to facilitate discussions with (b) (4), (b) (5) leadership.

Evaluating New SARS-CoV-2 Variants

Dr. (b) (6) met with BARDA, NIAID, FNIH, and CDC to discuss a comprehensive strategy to tackle new SARS-CoV-2 variants in the US, including: (1) surveillance, (2) testing of current vaccines and mAb therapeutics against known circulating variants, and (3) a prospective plan to address variant shift(s) that elude current mAbs. The ACTIV Preclinical WG intends to present its prospective plan to address SARS-CoV-2 variant shifts at a future TX-Clinical WG meeting. Rather than having the Preclinical WG members give two presentations, Dr. (b) (6) inquired whether the TOC would be willing to attend a TX-Clinical WG meeting, which is held Thursdays at 1 pm.

Dr. (b) (6) also noted the engagement of a mutation tracking expert will be discussed tomorrow during the Preclinical WG portion of the ACTIV Executive Committee-Leadership meeting. Dr. (b) (6) cannot attend, but Dr. (b) (6) will be in attendance. Dr. (b) (6) offered to share this plan with Dr. (b) (6) for her feedback.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)*

Emily Erbeling, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID, NIH*

James P. Kiley, PhD, *Director, Division of Lung Diseases, NHLBI, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert “Lynn” Marks, MD, *Senior Adviser to BARDA, Office of the Director*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Erica Ollmann Saphire, PhD, *Professor, La Jolla Institute for Immunology*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

Janet Woodcock, MD, *Therapeutics Lead, Operation Warp Speed*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, FDA*

Elizabeth Church, PhD, *Deputy Director, Therapeutics Research Program, DAIDS, NIAID, NIH*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Peter Stein, MD, *Director of the Office of New Drugs, FDA*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Helen Q. Chen, *Consultant, Deloitte*

Evan Appell, *Consultant, Deloitte*

Nada Saleh, *Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

(b) (6) to Everyone: 3:54 PM

I love the idea of a pragmatic trial. I do not think it is too late to help set that up.

(b) (6) to Everyone: 3:54 PM

That would be great. Some of these are so safe--ivermectin is given to whole islands, as you know (b) (6)

(b) (6) to Everyone: 3:54 PM

what would be best endpoint? hospitalization, yes/no?

(b) (6) to Everyone: 3:55 PM

yes, something very clear.

(b) (6) to Everyone: 3:55 PM

I want to echo (b) (6)'s comment. It doesn't make sense for the ACTIV Thx Prioritization group to act as a Guidelines group vs. having the guidelines group advise the ACTIV Therapeutics WG Prioritization group that there is a need.

(b) (6) to Everyone: 3:55 PM

In fact, we could take formal recommendations from the GLP to consider an agent for one of the ACTIV studies.

(b) (6) to Everyone: 3:55 PM

Hospitalizations for sure, but if we could get the ACTIV-2 study diary given out as an app, then you could get symptoms too.

(b) (6) to Everyone: 3:56 PM

The symptom score has not yet been accepted by FDA for outpatient.

(b) (6) to Everyone: 3:56 PM

Could we try to ask a trial like REMAP-CAP which is slightly more pragmatic? Would that be faster? Or are they limited to whatever is being studied globally?

(b) (6) to Everyone: 3:57 PM

There are so many challenges interpreting REMAP-CAP.

(b) (6) to Everyone: 3:57 PM

What about Google/Verily? They are pretty good at virtual trials and they have testing center tie ins.

(b) (6) to Everyone: 3:57 PM

They might work with us (b) (6)

(b) (6) to Everyone: 3:57 PM

Yes

(b) (6) to Everyone: 3:57 PM

The symptom score is not accepted as primary, but it has been accepted for graduation from phase 2 to 3

(b) (6) to Everyone: 3:58 PM

I think the challenge is clear data and results from simple well-done trials. (b) (4), (b) (5) is working in this space.

(b) (6) to Everyone: 3:59 PM

Trial in a box!

(b) (6) to Everyone: 4:01 PM

Yes, they are enrolling very well.

(b) (6) to Everyone: 4:01 PM

For SIREN: (b) (6) NINDS, (b) (6) at NHLBI, and to coordinate with our CONNECTS COVID efforts, (b) (6) at NHLBI should be looped into the discussions. (b) (6) and I can help as well.

(b) (6) to Everyone: 4:02 PM

NIAID is talking to (b) (4), (b) (5) regularly.

(b) (6) to Everyone: 4:03 PM

UK has an outpatient study, also cannot remember the names of the trial. I can also check with Solidarity on ivermectin.

(b) (6) to Everyone: 4:03 PM

I had a meeting with (b) (4), (b) (5)

ACTIV, Cross-Trial Operations Meeting

Thursday, January 7th, 2021

Action Items

Action Items		
	Information	Owner(s)
1.	Provide numbers for HHS Portal and Call Center Traffic.	Chris Shreeve

Meeting Summary

- ACTIV and Convalescent Plasma trials are going well and picking up speed; ACTIV-4c is still working to launch, but received drug this week.
- Portal and call center experienced (expected) dip in traffic over holidays; monoclonal antibody page will launch Friday, 01/08.
- PICS Contract has been awarded.
- OWS will work with NIH to develop Lesson Learned and utilize resources from both sides.

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Updates
- HHS Portal and Call Center Update
- PICS Contract Update
- Site Identification Efforts Update
- Pan-NIH Lessons Learned from Pandemic Response
- Remdesivir Supply Planning
- Meeting Recap

ACTIV and Convalescent Plasma Trials Status Update

- ACTIV-1: 23 sites open; (b) (4) as of 01/06
 - Submitted amendment 1 to IRB on December 3 and FDA on December 4
 - Has been accepted and is in the process of implementation
 - Conducted DSMB review on 01/07
 - Evaluating and selecting participating sites
- ACTIV-2: 89 sites open; (b) (4) as of 01/06
 - (b) (4) on 01/05 (now up to 8 patients); (b) (4) open label study to be closed after 01/15
 - Version 3.0 submitted to FDA on Dec.22; working in parallel on Version 4.0 (this cannot be submitted to CBER until CDER signs off on Version 3.0)
- ACTIV-3: 29 sites open (post initial close-down after (b) (4) ; (b) (4) as of 01/06 – anticipating to hit 450 patients last week of Jan./first week of Feb.
 - Version 3.0 submitted to the FDA and cIRB on 12/15 (AZ IV antibody cocktail)

ACTIV, Cross-Trial Operations Meeting

Thursday, January 7th, 2021

- ACTIV-3b/TESICO protocol reviewed by DSMB on Monday, 01/04
- ACTIV-4:
 - Hospitalized: 45 sites open; (b) (4) as of 01/06
 - DSMB met on 12/16 and recommended enrollment in moderately ill patients only
 - Pre-hospitalized: 10 sites open; (b) (4) as of 01/06
 - Post-hospitalized received first drug shipment on 01/05
 - ACTIV-4a and 4c on hold
- ACTIV-5 (Big Effect Trial): 9 sites open (goal = 40 sites); (b) (4) as of 01/06
 - Prioritizing additional investigational agents
- Convalescent Plasma Trials – enrolling well
 - CONTAIN COVID-19
 - 17 sites; (b) (4) as of 01/06 (target = 1,000 patients)
 - Next DSMB meeting 01/22; beginning to work on manuscript
 - Adding up to 13 more sites
 - PassItONII
 - 20 sites; (b) (4) as of 01/06 (target = 1,000 patients)
 - Next DSMB meeting on 01/26 – reviewed data from first 450 patients
 - Adding up to 13 more sites; working on manuscript – close to circulating a draft
 - Rationale and design manuscript in preparation
 - C3PO
 - 49 sites; (b) (4) as of 01/06
 - Adding up to 19 more sites
 - DSMB meeting held on 01/04; there were no safety concerns
 - Assessed sample size and there may be a need for additional participants (currently at 403 to a maximum of 900); everything is going fairly smoothly
 - Running out of placebo (yellow vitamin solution); considering giving saline

HHS Portal and Call Center Update (Chris Shreeve, OWS)

- Portal (Combat COVID Website) has transferred to OWS and NIH so direct control over that now; as changes come in, they get done immediately – feel free to send updates and changes and those will get done immediately
- There was a dip in traffic to the portal/call center over the holiday season (the call center lead at PPD said this is to be expected); Chris will bring numbers next meeting (they come in on Tuesdays)
- Worked on getting the monoclonal antibody page up over the holidays; this will launch tomorrow and will help health care providers find resources in their states.
- Primary goal right now is to get people to the website as soon as we can so that we can direct them to the call center and to the studies

PICS Contract Update (Avon Cornelius, HHS)